Aalto University School of Chemical Engineering

Department of Chemistry and Materials Science

and

Université catholique de Louvain

Institute of Condensed Matter and Nanosciences

Molecular Chemistry, Material and Catalysis

Towards the Total Synthesis of Manzaminoïds

Laurent Gillard

A doctoral dissertation completed under joint supervision cotutelle agreement to be defended for the degree of Doctor of Science (Technology) from Aalto University, and the degree of Docteur en Sciences from Université catholique de Louvain. The public examination will be held at Auditoire LAVO 51 – Place Louis Pasteur, 1 - 1348 Louvain-la-Neuve, Université catholique de Louvain on the 1st of February 2019 at 16:00, and on-line connection for Aalto University will be shown at Ke5 lecture hall, Kemistintie 1, Espoo.

Louvain-la-Neuve

February 2019

Supervising professors

Prof. Ari Koskinen, Aalto University and Prof. Olivier Riant, UCLouvain

Thesis advisors

Dr. Geoffrey Solberghe (UCB) and Dr. Raphaël Dumeunier (Syngenta)

Preliminary examiners

Prof. Donald Craig, Imperial College London, UK

Prof. Nicholas J. Turner, University of Manchester, UK

Opponents

Prof. Janine Cossy, the Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI ParisTech), France

Prof. Donald Craig, Imperial College London, UK

Aalto University publication series
DOCTORAL DISSERTATIONS 19/2019

ISBN 978-952-60-8400-8 (printed)
ISBN 978-952-60-8401-5 (pdf)
ISSN 1799-4934 (printed)
ISSN 1799-4942 (pdf)

Université catholique de Louvain publication series
DOCTORAL DISSERTATIONS
Numéro de collection: 511
Domaine: SC

Jury Members

Prof. Yann Garcia (UCLouvain, President/Chairman)

Prof. Janine Cossy (Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris (ESPCI ParisTech), France)

Prof. Nicholas J. Turner (University of Manchester, UK)

Prof. Donald Craig (Imperial College London, UK)

Prof. Michael L. Singleton (UCLouvain, Secretary)

Prof. Ari M. P. Koskinen (Aalto University, Finland, Supervisor)

Prof. Olivier Riant (UCLouvain, Supervisor)

Prof. István E. Markó (†) (UCLouvain, Supervisor)

Aalto University

Aalto University, P.O. Box 11000, FI-00076 Aalto
www.aalto.fi

Abstract

Author
Gillard Laurent

Name of the doctoral dissertation
Towards the Total Synthesis of Manzaminoids

Publisher School of Chemical Technology

Unit Department of Chemistry

Series Aalto University publication series DOCTORAL DISSERTATIONS 19/2019

Field of research Organic Chemistry

Manuscript submitted 12 October 2018 **Date of the defence** 01 February 2019

Permission to publish granted (date) 26 November 2018 **Language** English

☒ **Monograph** ☐ **Article dissertation** ☐ **Essay dissertation**

Abstract

For the last decades, our laboratory has been interested in the development of new synthetic methodologies and their application to the total syntheses of natural products exhibiting biological activities. In this context, our investigation focused on the conception of new potential bioactive manzamine derivatives. For this purpose, new molecules were synthetized using novel approaches of anionic polycyclization. Three methodologies were developed allowing to reach our targets. On top of that, some mechanistical analyses were made to rationalize the observed diastereoselectivities. Finally, the derivatisation of some target molecules allowed us to quickly extend our library of bioactive compounds.

Keywords Manzamine, Polycyclization

ISBN (printed) 978-952-60-8400-8 **ISBN (pdf)** 978-952-60-8401-5

ISSN-L / **ISSN (printed)** 1799-4934 **ISSN (pdf)** 1799-4942

Location of publisher Helsinki, Finland **Location of printing** Louvain-la-Neuve, Belgium **Year** 2019

Pages 386 **urn** /

This thesis is dedicated to the people who supported the creation of this work but who will never get the opportunity to read it.

Boss, my father & grand-parents

"You can add one more year of PhD for each nitrogen present in your natural molecule"

Unknown

"Ce projet secondaire prendra au maximum deux semaines."

I. E. M.

Remerciements & Acknowledgements

Après une décennie aux “études” il y a forcément pas mal de personnes à remercier.

Tout d’abord le professeur Markó aka BOSS sans qui mon goût pour la chimie organique et même ce document n’existerait pas. Qui nous donnait des exercices « faciles » et ne posait que des questions « simples ». Le but étant de développer notre esprit critique et connaitre la limite de nos acquis. Mais le Boss c’était bien plus qu’un superviseur aux yeux de beaucoup, toujours de bonne humeur et toujours motivé. En plus des échanges intellectuels quasi-quotidien, il y avait les discussions enflammées sur les ours polaires, les piles, le climat, la viande, … le tout sur le temps de midi. Pour tous les bons moments passés en sa présence, je l’en remercie !

I would like to thank Professor Ari Koskinen for his warm welcome to his group and who allowed me to finish this work. And also, for the scientific and non-scientific discussions during my last year of thesis.

Je voudrais aussi remercier le Professeur Riant qui m’a permis de continuer ce projet.

I would like to thank my jury (Prof. Garcia, Prof. Cossy, Prof. Turner, Prof. Craig, Prof. Singleton) for their time, expertise, evaluation and the discussions.

Merci à Pol pour les corrections et le temps passé. Je t’ai fait souffrir, je le sais.

Rien n’est possible dans le labo sans un certain Fabio. Technicien, RH, électricien, assistant de plateau télé, manutentionnaire, déménageur, comptable, plombier, web master, … Bref, il a toutes les casquettes. Toujours

de bon conseil quand il s'agit de chimie, il a été un excellent maitre d'équipage durant mon temps dans le labo du Boss. Merci beaucoup.

Merci aux personnels de l'UCL et Aalto pour leurs aides (analyses, paperasses, autres …) Mais tout particulièrement Chanchan, Audrey, Corinne et Sirje sans qui je serai encore occupé avec les papiers.

Ces années de thèse n'auraient pas été les mêmes sans Jean-Boris dit Bobo Le maitre des lactones, Jérôme (prononcé comme Brian Stoltz) et Akin le mangeur de saucisson. Mais aussi les « vieux », Kevin, J-F, Pol, et Thomas. Of course, the entire Chinese family: Yazhou, Lei, Qian, Xiao, Amaury and Jérémie. It was really pleasant to spend time with all of you during few years.

Of course, I would feel guilty to not mention the Koskinen group with Saara, Anna-Kaisa, Eemil (alone surrounded by girls in his office), Madga (you can finish it), and Olga who was always in good mood. Finally, the German part, Christina, Fabian, Jan and Janne (now you are German). The time spent with you in Finland was way too short. Special thanks go to Saara who introduced me to the Finnish culture.

I would like to thank my friends who supported me and who kept on asking me the same question for four years « So, what are you doing? ». The small girl in Austria, the blond girl in Helsinki, the Portuguese girl, les gens du Gaudé, ceux coincés à BXL et enfin ceux originaires de Mouscron.

Finalement, je voudrais remercier ma famille qui m'a supportée pendant toutes ces années. Et particulièrement, Maman et Papy sans qui je n'aurais sûrement pas fait ces choix et merci d'avoir cru en moi.

Author's contribution

The Author has designed and carried out the experiments, recorded the analytical data and interpreted the results that are presented in this thesis with the following exceptions:

The elemental and mass spectroscopic experiments were recorded by Mr. Raoul Rozenberg (UCLouvain) or Ms. Heidi Meriö-Talvio (Aalto University).

Crystallographic data was collected by Dr. Martin Nieger (University of Helsinki, Finland).

The Author and the supervisor Prof. Ari Koskinen planned and discussed the simulations.

The Author and the supervisor Prof. István E. Markó (†) conceived the project.

List of abbreviations

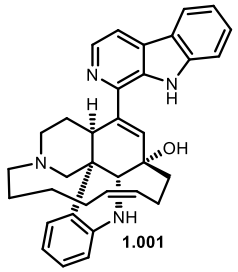
°C	Celsius degree
α	Alpha
β	Bêta
Δ	Delta
δ	Delta
σ	Sigma
Å	Ångström
Ac	Acetyl
AIBN	Azobisisobutyronitrile
Bn	Benzyl
Boc	*tert*-butyloxycarbonyl
BOPCl	Bis(2-oxo-3-oxazolidinyl)phophinic chloride
Bu	butyl
CAN	Ceric ammonium nitrate
CDI	Carbonyldiimidazole
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DCE	Dichloroethane
DCM	Dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DiBAL-H	Diisobutylaluminum hydride
DIPEA	Di-*iso*-propylethylamine
DMAP	4-Dimethyl aminopyridine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
ee	Enantiomeric excess
Et	Ethyl
Eq.	Equivalent
FGAP	Fourth Generation Anionic Polycyclization
HMBC	Heteronuclear Multiple Bond Correlation

HMDS	Bis(trimethylsilyl)amine
HRMS	High resolution mass spectrometry
Hz	Hertz
IBX	2-iodoxybenzoic acid
IC_{50}	Half maximal inhibitory concentration
*i*PrOH	*iso*-propanol
IR	Infrared spectroscopy
kJ	kilo Joule
LAH	Lithium aluminum hydride
LDA	Lithium di-*iso*-propylamide
LiTMP	Lithium tetramethylpiperidide
M	Molar
*m*CPBA	*meta*-chloroperoxybenzoic acid
MIC	Minimum inhibitory concentration
MP	Melting point
Ms	Mesyl
MS	Mass spectrometry
MS 4Å	Molecular sieves 4 Ångström
NMM	N-methylmorpholine
NMR	Nuclear Magnetic Resonance Spectroscopy
NOE	Nuclear Overhauser Effect
NOESY	Nuclear Overhauser Effect Spectroscopy
Ns	Nosyl
Nu	Nucleophile
Pd/C	Palladium on Carbon
Ph	Phenyl
pharM	Photocycloaddition/retro-Mannich fragmentation/Mannich closure cascade
PMB	*para*-methoxybenzyl
PMPOH	*para*-methoxyphenol
PPTS	Pyridinium *para*-toluenesulfonate
PTSA	*para*-toluene sulfonic acid
RCM	Ring-closing metathesis
RT	Room Temperature

SGAP	Second generation anionic polycyclization
TBAF	Tetra-*n*-butylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butylhydroperoxide
Teoc	Trimethylsilylethoxycarbonyl
Tf	Triflyl
TFA	Trifluoracetic acid
TFAA	Trifluoroacetic anhydride
TGAP	Third Generation Anionic Polycyclization
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMG	Tetramethylguanidine
TMS	Trimethylsilyl
TRIS	Tris(hydroxymethyl) aminomethane
TS	Transition state

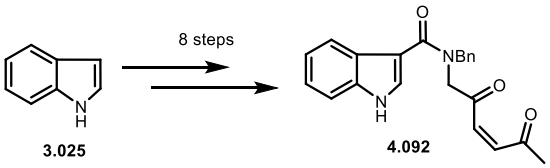
Summary

Our laboratory has been interested in the development of new methodologies and their application to total syntheses of natural products for many years. In this context, this work started with an investigation on a new polycyclization methodology targeting indole manzamine **1.001** (Scheme 1).



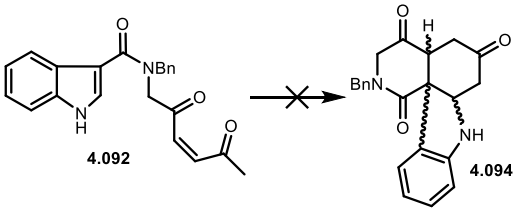
Scheme 1: Indole manzamine

On our endeavour toward the polycyclization precursor, many issues were encountered and were successfully solved. Besides this, the first precursor **4.092** was obtained after 8 steps from indole **3.025** (Scheme 2).



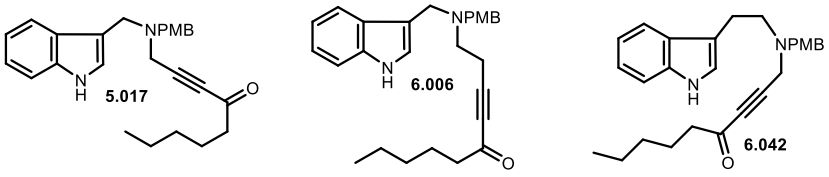
Scheme 2: Synthesis of *Z*-ene-dione 4.092

The polycyclization attempts of 4.092 were unsuccessful so far in the presence of organic bases, strong bases and Lewis acids and regrettably, no tetracycle **4.094** were observed (Scheme 3).



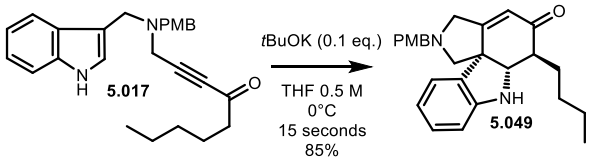
Scheme 3: Polycyclization attempts

The reaction and precursors were redesigned and modified towards ynone derivatives. Three different substrates were synthetized **5.017**, **6.006** and **6.042** using simple synthetic steps from indole or tryptamine (Scheme 4).



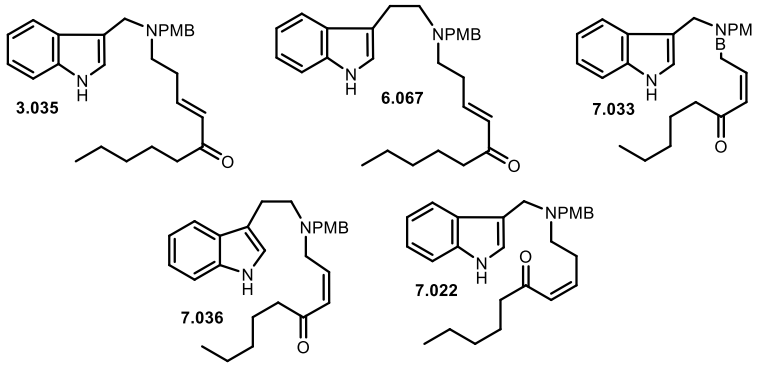
Scheme 4: Ynone precursors

New polycyclization conditions were found and optimized to turn **5.017** into one single diastereoisomer of compound **5.049**. The same conditions were ineffective on **6.006** and **6.042** and some mechanistical analyses were made to understand the difference between those compounds (Scheme 5).



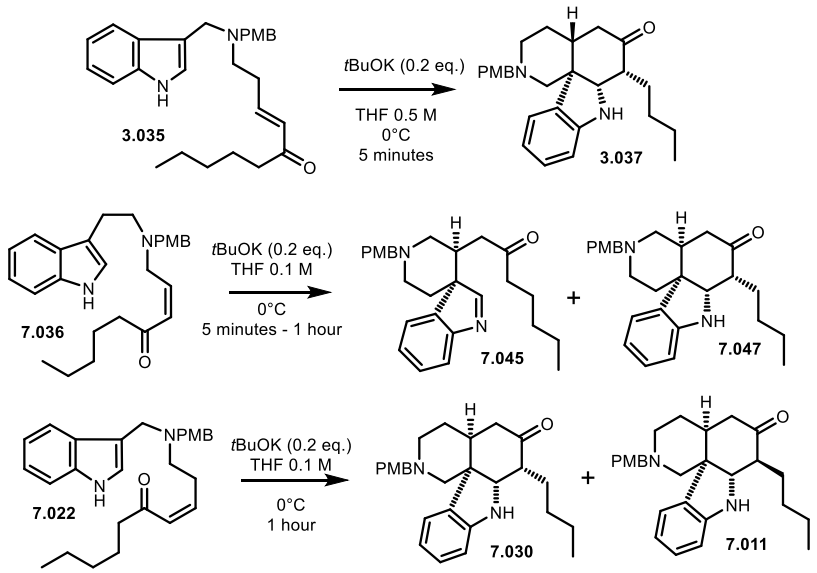
Scheme 5: Polycyclization of ynone

To increase the scope of the methodology, some tests were performed on other substrates such as *E*-enone **6.059** and **6.067** or *Z*-enone **7.033**, **7.036** and **7.022** (Scheme 6).



Scheme 6: *E*-enones and *Z*-enones

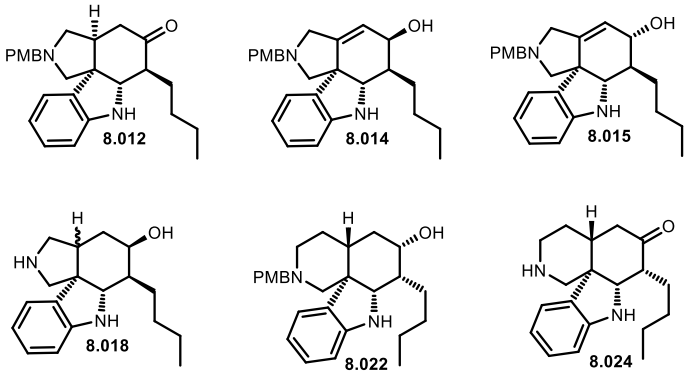
New scaffolds **3.037**, **7.045**, **7.047**, **7.030** and **7.011** were obtained, using the developed polycyclization conditions. Different mechanisms were proposed to explain the diastereoselectivities of those transformations (Scheme 7).



Scheme 7: Polycyclizations of new precursors

Finally, one of the main objectives of this thesis was to create a library of compounds that should be submitted to biological testing. To do so, diastereocontroled derivatizations were performed on the described tetracycles **5.049** and **3.037**. Among the new products, ketone **8.012** embeds

the desired stereochemistry in its backbone, similar to the one of **1.001**. The rest of the library offers a wide panel of scaffolds such as **8.014**, **8.015**, **8.018**, **8.022**, **8.024** (Scheme 8).



Scheme 8: Diastereocontrolled derivatisation

Résumé

Depuis des années, notre laboratoire s'est intéressé au développement de méthodologies ainsi qu'à leur application en synthèse totale de produit naturel. C'est dans cette optique de travail que démarre ce projet sur le développement d'une nouvelle méthode de polycyclisation pour atteindre le dérivé manzamine indolique **1.001** (Schéma 1).

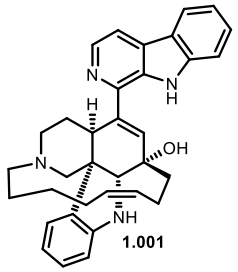


Schéma 1: Manzamine indolique

En chemin pour le premier précurseur de polycyclisation différents problèmes synthétique ont été rencontré et surmonté. Pour amener à une synthèse assez rapide du précurseur **4.092** en 8 étapes au départ d'indole **3.025** (Schéma 2Scheme 2).

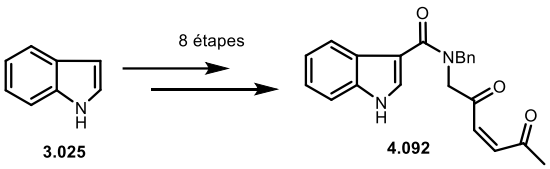


Schéma 2: Synthèse de Z-éne-dione 4.092

Les tests de polycyclisation ont été infructueux dans l'obtention d'un tetracycle de type **4.094** en utilisant des bases fortes ou des acides de Lewis (Schéma 3).

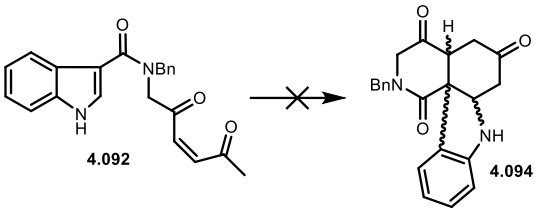


Schéma 3: Tentatives de polycyclisation

Une reconsidération de la réaction et des précurseurs a été effectuée pour valoriser et essayer les dérivés de type ynone. Trois de ces composés ont été synthétisés **5.017**, **6.006** and **6.042** au départ d'indole ou de tryptamine (Schéma 4).

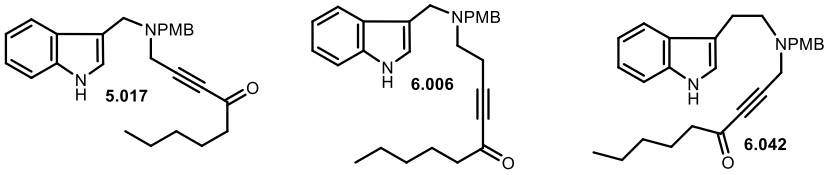


Schéma 4: Précurseurs ynone

De nouvelles conditions de polycyclisation ont été découverte et optimisée pour transformer **5.017** dans le tétracycle **5.049** de façon diastéréocontrollée. Les mêmes conditions ont été inefficace sur les deux autres substrats **6.006** et **6.042**. Différentes hypothèses mécanistiques ont été proposées pour expliquer cette modification de réactivité (Schéma 5).

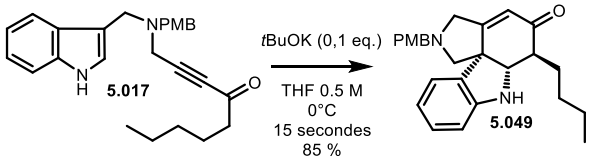


Schéma 5: Polycyclisation d'ynone

Pour améliorer la compréhension de notre méthodologie, plusieurs tests ont été effectués sur d'autres substrats parmi lesquels, *E*-enone **6.059** et **6.067** ou encore *Z*-enone **7.033**, **7.036** et **7.022** (Schéma 6).

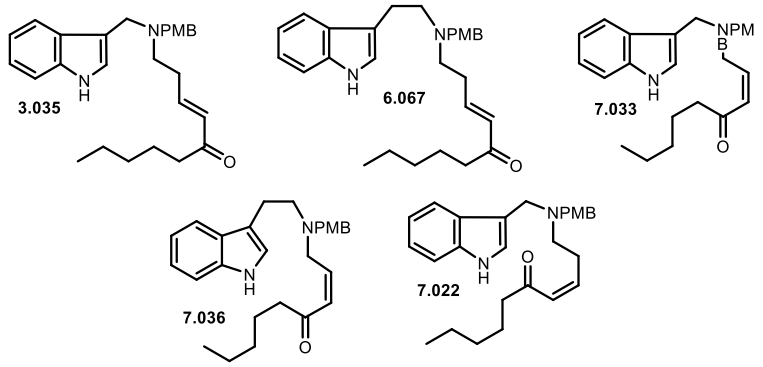


Schéma 6: *E*-enones et *Z*-enones

De nouvelles structures ont été obtenues grâce aux conditions de polycyclisation **3.037**, **7.045**, **7.047**, **7.030** et **7.011**. Plusieurs mécanismes ont été proposés pour expliquer la différence de diastéréosélectivité de ces réactions (Schéma 7).

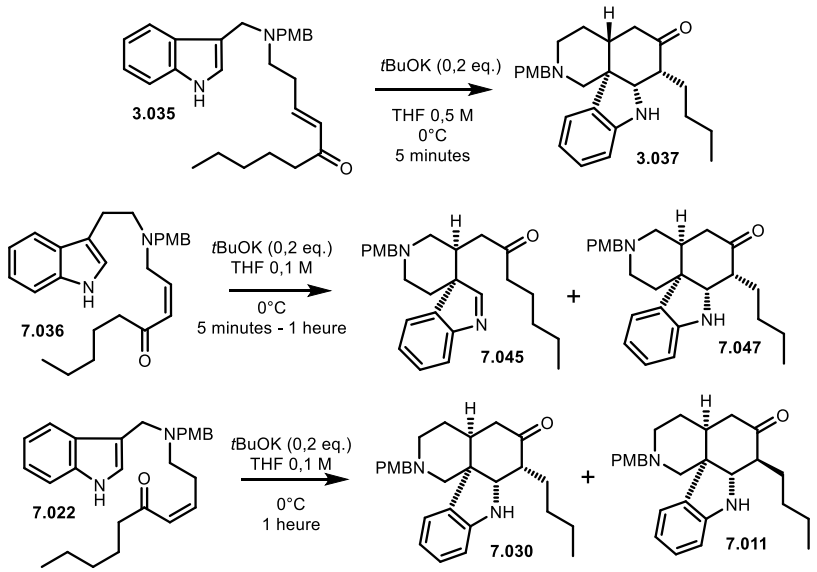


Schéma 7: Polycyclisation des nouveaux précurseurs

L'un des objectifs principaux de ce projet était la création d'une bibliothèque de composés pour tester les activités biologiques. Pour mettre en place ceci, nous avons eu recours à différente méthodes de dérivatisations diastéréocontrollées à partir des tétracycles **5.049** et **3.037**.

Parmi les nouveaux produits, on peut trouver la cétone **8.012** qui possède les quatre centres stéréogéniques requis. Les restes de la bibliothèque offre un panel varié de structures tel que **8.014**, **8.015**, **8.018**, **8.022**, **8.024** (Schéma 8).

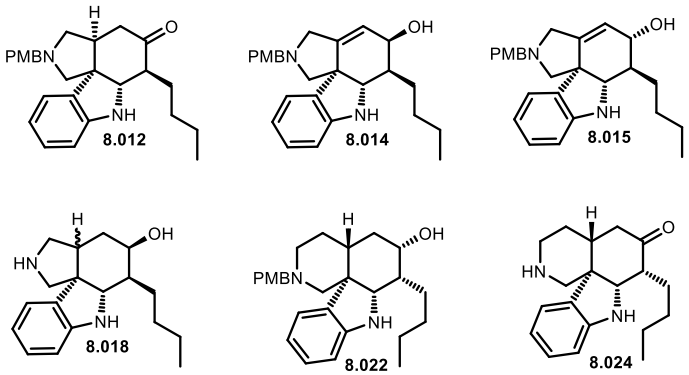


Schéma 8: Dérivatisation diastéréocontrollée

Table of contents

Chapter I

Manzamines Discovery and Bioactivities

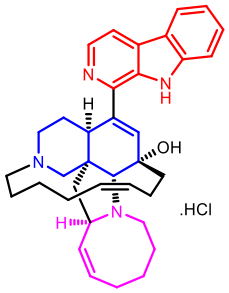
For decades, natural products chemists have been enthusiastic about complex molecules originating from marine organisms. Their remarkable structural features, properties and their scarcity make them very interesting and ambitious synthetic challenges for the scientific community.

1. Discovery

In 1986, Sakai and Higa discovered a new type of alkaloid inside the genus *Haliclona* marine sponge from Manzamo, next to Okinawa, Japan (136 ppm from wet weight). The 3D structure of the hydrochloride salt of manzamine A **1.001** was resolved by Jefford and Bernardinelli using X-ray diffraction.

In the remarkable octa-cyclic structure were embedded fragments such as beta-carboline (in red), an octahydroisoquinoline central core (in blue) and a thirteen membered ring (in blue and black). On top of that, the fearsome natural product encompassed a hexahydroazocine (in pink) and a pyrrolidine. Further structural complexity was introduced *via* a tertiary alcohol, five chiral centres and three unsaturations (Scheme 1).[1]

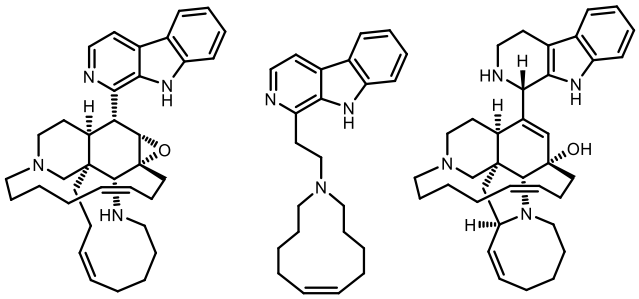
[1] Sakai, R.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *J. Am. Chem. Soc.* **1986**, *108*, 6404.



manzamine A
1.001

Scheme 1: Manzamine A

Furthermore, this new compound exhibited many interesting bioactivities (see page 15). Therefore, interest was initiated in many synthetic and natural products groups. Only one year after its initial discovery the same group revealed three new scaffolds in the same genus of sponge: manzamine B **1.002** (16 ppm from wet weight), manzamine C **1.003** (11 ppm from wet weight) and manzamine D **1.004** (Scheme 2).[2]



manzamine B
1.002

manzamine C
1.003

manzamine D
1.004

Scheme 2: Manzamine B, C, D

Like manzamine A **1.001**, those new molecules **1.002**, **1.003**, **1.004** possess various bioactivities. However, their scaffold was slightly different from **1.001**:

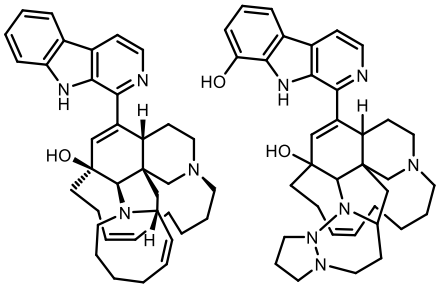
[2] Sakai, R.; Kohmoto, S.; Higa, T.; Jefford, C. W.; Bernardinelli, G. *Tetrahedron Lett.* **1987**, *28*, 5493.

Manzamine B **1.002** own an eleven membered ring at the bottom, an epoxide at the central core and six chiral centres instead of five.

Manzamine C **1.003** is a carboline with an eleven membered ring but does not possess the fused ring complexity of manzamine A **1.001** or B **1.002**.

Manzamine D **1.004** strongly resembles manzamine A **1.001**, except for the oxidation state of the β-carboline which is a tryptoline derivative.

In 1987, Jun'ichi Kobayashi *et al.* found similar products in genus *Pellina* marine sponge; keramamine A **1.005** (260 ppm from wet weight) and keramamine B **1.006** (480 ppm from wet weight) (Scheme 3).[3]

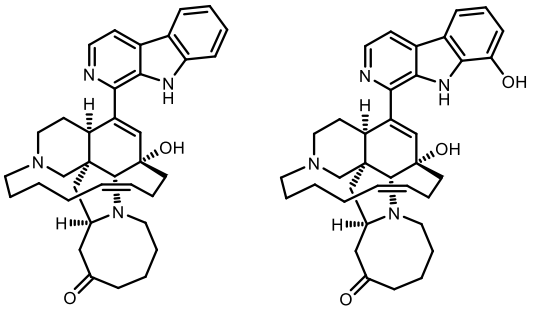


Scheme 3: Keramamine A and B

In 1988, Higa *et al.* discovered new compounds in the genus *Xestospongia.* This new publication acted as an **erratum** for keramamines A **1.005** and B **1.006**, which were proven to be, respectively, manzamine A **1.001** and manzamine F **1.008** (18 ppm from wet weight). Manzamine E **1.007** (5 ppm from wet weight) was also reported (Scheme 4).[4]

[3] Nakamura, H.; Deng, S.; Kobayashi, J.; Ohizumi, Y.; Tomotake Y.; Matsuzaki, T.; Hirata, Y. *Tetrahedron Lett.* **1987**, *28*, 621.

[4] Ichiba, T.; Sakai, R.; Kohmoto, S.; Saucy, G.; Higa, T. *Tetrahedron Lett.* **1988**, *29*, 3083.



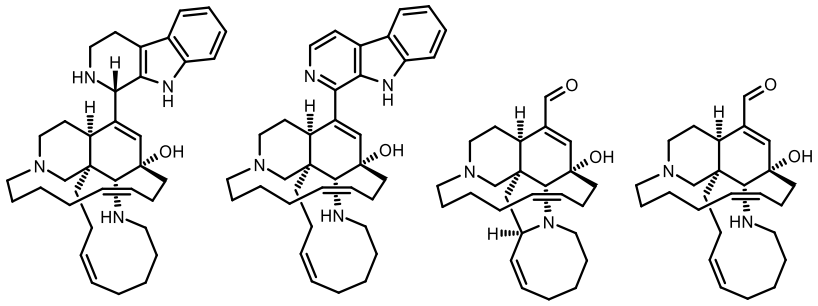
Scheme 4: Manzamines E and F

Manzamine E **1.007** is an oxidized version of manzamine A **1.001** with an azocinone moiety instead of an azocine.

Manzamine F **1.008** is an oxidized version of manzamine E **1.007** with a modified β-carboline.

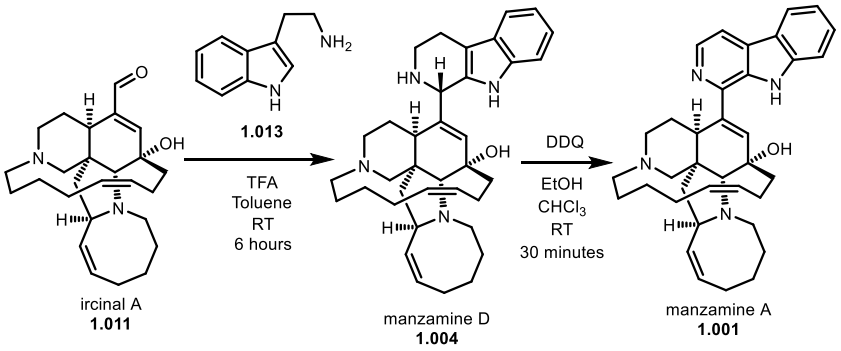
In 1992, Kobayashi *et al.* isolated four new molecules from the genus *Ircinia*: manzamine H **1.009** (7 ppm from wet weight), manzamine J **1.010** (22 ppm from wet weight), ircinal A **1.011** (57 ppm from wet weight), ircinal B **1.012** (20 ppm from wet weight). The detection of **1.009** and **1.010** tends to prove that there are two classes of manzamines, the first is designed on manzamine A **1.001** (including manzamines D, E, F which possess a fused pyrrolidine-azocine ring) and the other on manzamine B **1.002** (including manzamines H, J which possess a 11-membered ring) (Scheme 5).[5]

[5] Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.



Scheme 5: Manzamines H and J, ircinals A and B

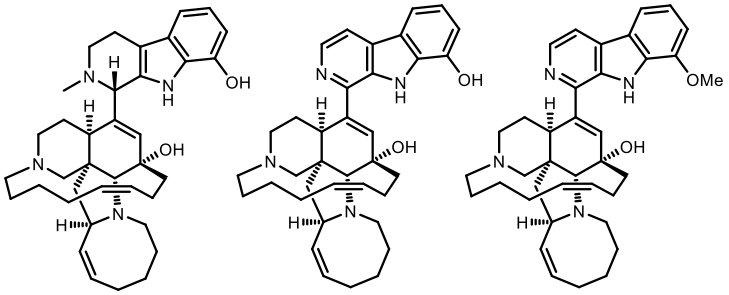
As new features, ircinal A **1.011** and B **1.012** are interesting and probably biosynthetic precursors of manzamines. Kobayashi *et al.* brought to light this possibility with a Pictet-Spengler reaction from ircinal A **1.011** to manzamine D **1.004** then oxidation with DDQ to obtain manzamine A **1.001**. The same experiment was conducted from ircinal B **1.012** to manzamine J **1.010** (Scheme 6).



Scheme 6: Pictet-Spengler and oxidation towards manzamine A

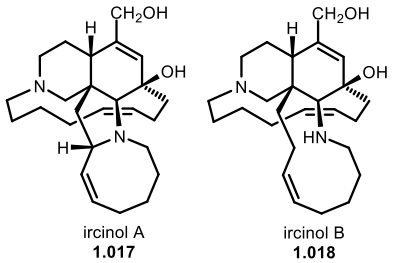
In 1994, different groups observed new β-carboline modifications in manzamine such as **1.014** (1700 ppm from wet weight), manzamine G **1.015** (3000 ppm from wet weight) and **1.016**. They were found in the genera

Pachypellina, Petrosia and *Cribochalina* (manzamine G **1.015** was referred as 8-hydroxy-manzamine A) (Scheme 7).[6]



Scheme 7: Manzamine G, and other derivatives

Also, in 1994, Jun'ichi Kobayashi *et al.* extracted ircinol A **1.017** and ircinol B **1.018** from marine sponge *Amphimedon*. Surprisingly, they are enantiomers of the standard scaffold of ircinal A **1.011** (40 ppm from wet weight) and B **1.012** (3 ppm from wet weight) from the genus *Ircinia* (Scheme 8).[7]



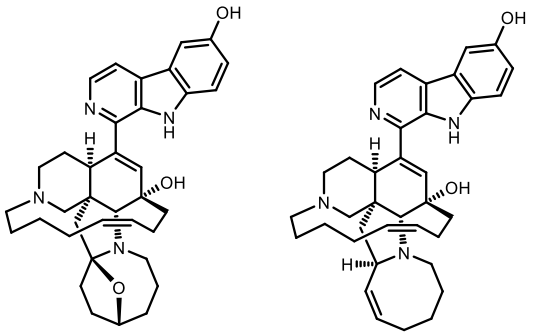
Scheme 8: Ircinols A and B

In 1995, Isao Kitagawa *et al.* found manzamine X **1.019** (2 ppm in wet weight) and manzamine Y **1.020** (2 ppm in wet weight) in marine sponges of the genera *Xestospongia* and *Haliclona*. Manzamine X **1.019** exhibits a new feature since the eight membered ring contains an ether bridge while the

[6] (a) Ichiba, T.; Corgiat, J. M.; Scheuer, P. J. *J. Nat. Prod.* **1994**, *57*, 168. (b) Crews, P.; Cheng, X. C.; Adamczeski, M.; Rodriguez, J.; Jaspars, M.; Schmitz, F. J.; Traeger, S. C.; Pordesimo, E. O. *Tetrahedron*, **1994**, *50*, 13567.

[7] Tsuda, M.; Kawasaki, N.; Kobayashi, J. *Tetrahedron*, **1994**, *50*, 7957.

manzamine Y **1.020** is an oxidized version of manzamine A **1.001** (Scheme 9).[8]



Scheme 9: Manzamines X and Y

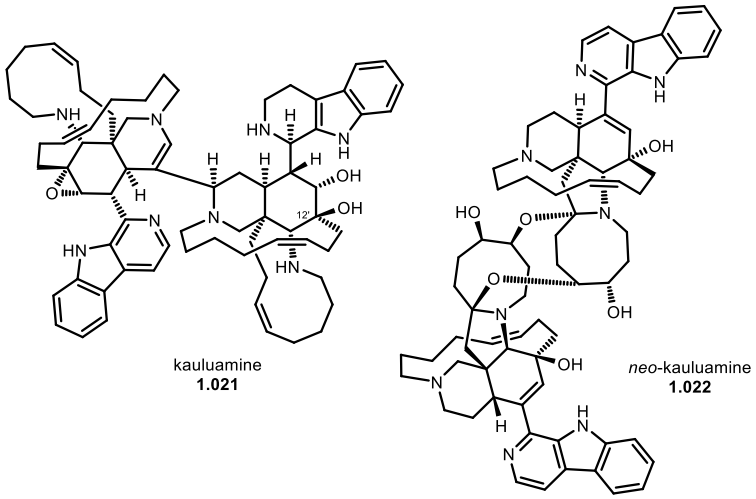
The complexity encountered in the manzamine family culminates with kauluamine[9] **1.021** (760 ppm from dry weight inside *Prianos* sp.) and *neo*-kauluamine **1.022** (48 ppm from wet weight inside *Prianos* sp.)[10] (10 ppm from wet weight inside *Acanthostrongylophora* sp.).[11] Both are dimers of manzamines, kauluamine **1.021** possesses two manzamine B **1.002** scaffolds with a total of 14 chiral centres, 14 cycles including two 13-membered rings and two 11-membered rings. One of the 13-membered rings was established to be antipodal at C12' from the classic manzamine core. *Neo*-kauluamine **1.022** is based on manzamine A **1.001** skeleton with a total of 14 chiral centres, 17 cycles including two 13-membered rings, one 11-membered ring and two 8-membered rings (Scheme 10).

[8] Kobayashi, M.; Chen, Y. J.; Aoki, S.; In, Y.; Ishida, T.; Kitagawa, I. *Tetrahedron*, **1995**, *51*, 3727.

[9] Ohtani, I. I.; Ichiba, T.; Isobe, M.; Kelly-Borges, M.; Scheuer, P. J. *J. Am. Chem. Soc.* **1995**, *117*, 10743.

[10] El-Sayed, K. A.; Kelly, M.; Kara, U. A. K.; Ang, K. K. H.; Katsuyama, I.; Dunbar, D. C.; Khan, A. A.; Hamann, M. T. *J. Am. Chem. Soc.* **2001**, *123*, 1804.

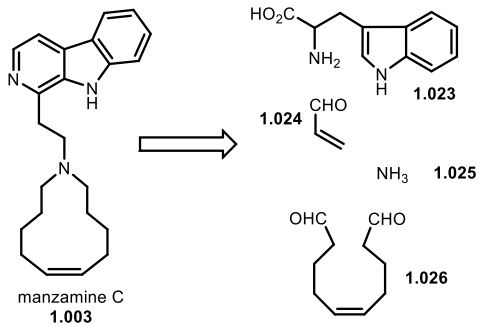
[11] El-Desoky, A. H.; Kato, H.; Eguchi, K.; Kawabata, T.; Fujiwara, Y.; Losung, F.; Mangindaan, R. E. P.; de Voogd, N. J.; Takeya, M.; Yokosawa, H.; Tsukamoto, S. *J. Nat. Prod.* **2014**, *77*, 1536.



Scheme 10: Kauluamine and *neo*-kauluamine

2. Biosynthesis

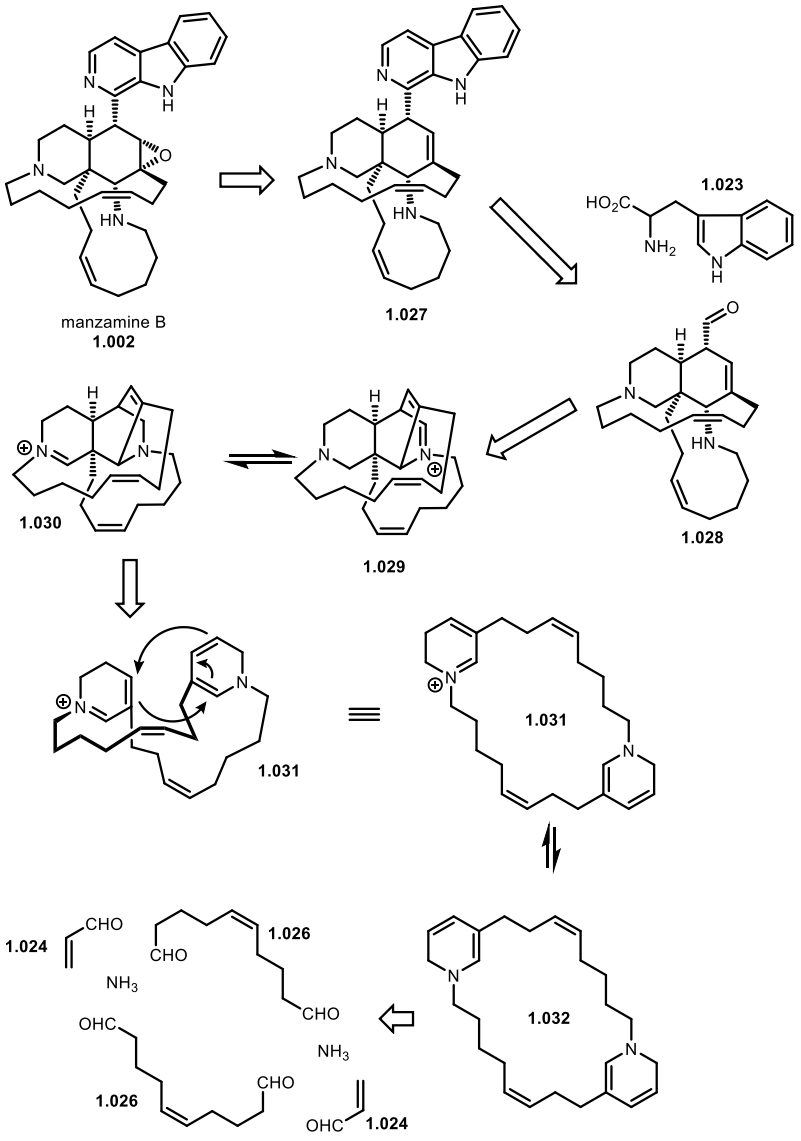
Through the years many groups have tried to elucidate the biological origin of manzamines. In 1992, Baldwin and Whitehead proposed a simple disconnection for the biosynthesis.[12] Only four different units were required, tryptophan **1.023**, an acrolein equivalent **1.024**, ammonia **1.025** and dialdehyde **1.026**. Applied on manzamine C **1.003** this protocol retrosynthetically required only reductive coupling of **1.026** with ammonia, followed by Michael addition and finally, a Pictet-Spengler like reaction to obtain this target **1.003** (Scheme 11).



Scheme 11: Potential biosynthetic pathway for manzamine C

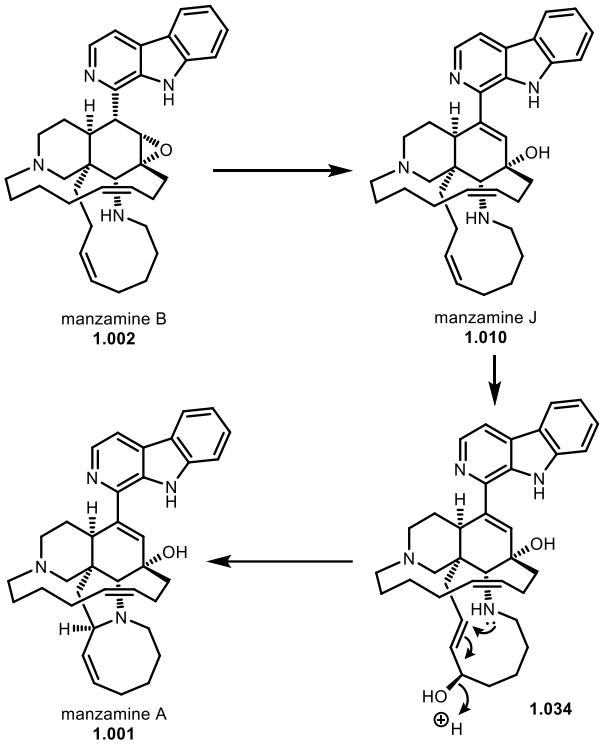
The construction of the core of manzamine B **1.002** could be performed also from the same units. Deoxygenation of manzamine B **1.002** followed by removal of tryptophan unit **1.023** leads back to an aldehyde **1.028** retrosynthetically closed to the iminium salt **1.029**. Redox exchange between the two piperidine rings of **1.029** give **1.030**, which is immediately revealed as the Diels-Alder adduct of bis-dihydropyridine **1.031**, a tautomer of the symmetrical species **1.032**. In turn, **1.032** is revealed as the reductive coupling product of two equivalents of dialdehyde **1.026** and two equivalents of acrolein **1.024** with two molecules of ammonia. The full relative stereochemistry and connectivity of manzamine B **1.002** follows from the expected endo and regiochemical preference of the Diels-Alder step (Scheme 12).

[12] Baldwin, J. E.; Whitehead, R. C. *Tetrahedron Lett.* **1992**, *33*, 2059.



Scheme 12: Potential biosynthetic pathway for manzamine B

Finally, manzamine A **1.001** is simply related to manzamine B **1.002** by a *trans*-eliminative opening of the epoxide and allylic oxidation of a double bond, followed by ring closure (Scheme 13).



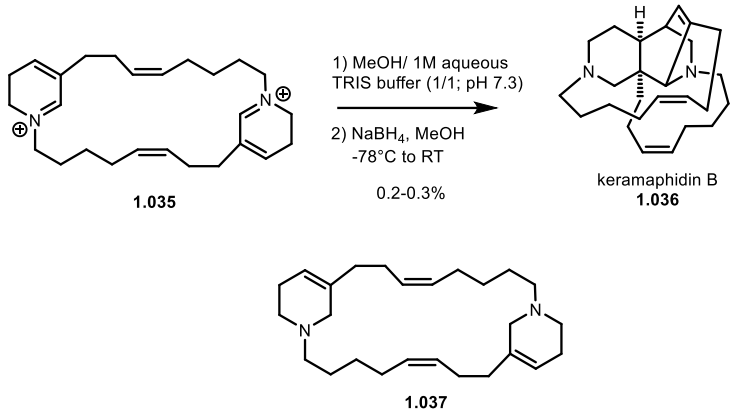
Scheme 13: Potential biosynthetic pathway for manzamine A

In 1998, to prove the viability of their hypothesis, Baldwin *et al*.[13] conducted a biomimetic synthesis of their proposal. In few steps, the authors created bis-dihydropyridinium **1.035** and cyclised it to **1.036** in 0.2-0.3 % yield. The main portion (between 60 and 85 %) of starting material disproportionated towards **1.037**. Interestingly, in 1994, keramaphidin B **1.036** was isolated by Kobayashi *et al*.[14] (30 ppm from wet weight inside

[13] (a) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Smrcková, S.; Whitehead, R. C. *Tetrahedron Lett.* **1996**, *37*, 6919. (b) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C.; Boughtflower, R. J.; Mutton, I. M.; Upton, R. J. *Angew. Chem. Int. Ed.* **1998**, *37*, 2661. (c) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead *Chem. Eur. J.* **1999**, *5*, 3156.

[14] Kobayashi, J.; Tsuda, M.; Kawasaki, N.; Matsumoto, K.; Adachi, T. *Tetrahedron Lett.* **1994**, *35*, 4383.

Amphimedon sp.) and Andersen *et al*.[15] (85 ppm from wet weight inside *Xestospongia* sp.). This is an evidence that no "Diels-Alderase" would be needed to perform the Diels-Alder reaction. A simple conformation provided by an enzyme should be enough and would probably also reduce the disproportionation towards **1.037** (Scheme 14).

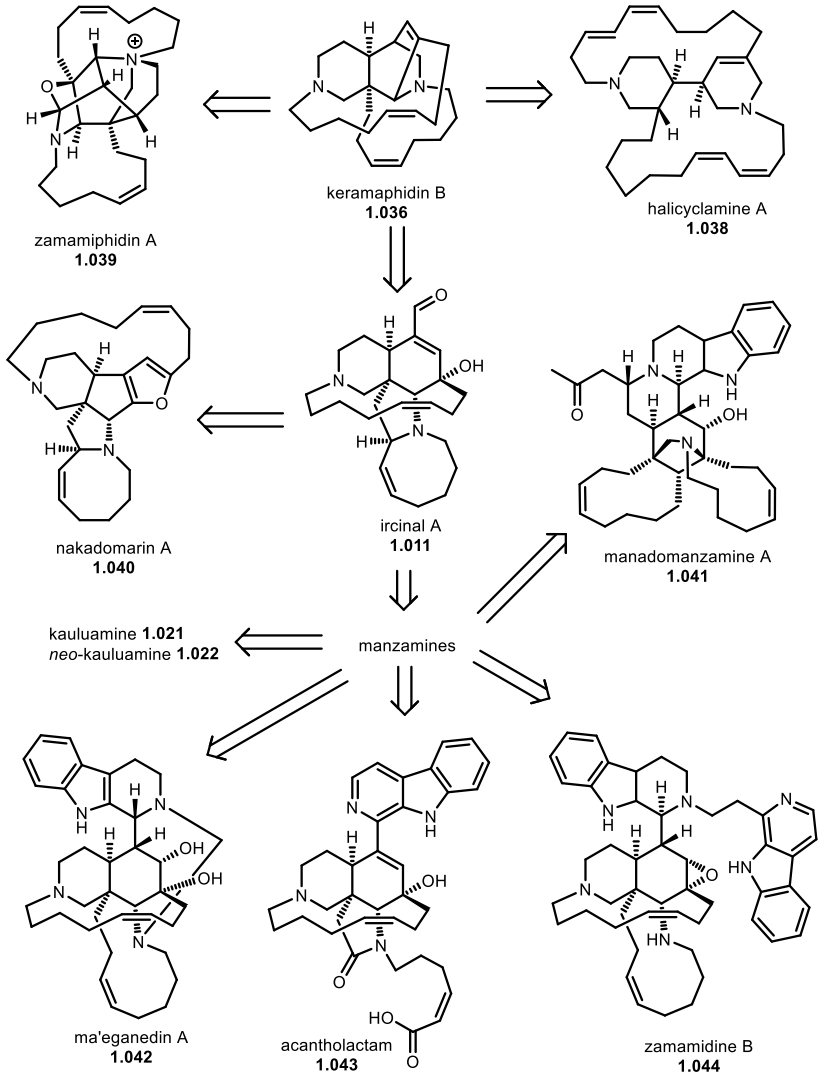


Scheme 14: Proof of hypothesis

Keramaphidin B **1.036** was suspected to be a key adduct in many biogenetic origins of manzamine derivatives such as halicyclamine A[16] **1.038** (29 ppm from wet weight inside *Xestospongia* sp.) and zamamiphidin A[17] **1.039** (1 ppm from wet weight inside *Amphimedon* sp.). Ircinal A **1.011** is probably the biogenic precursor of nakadomarin A[18] **1.040** (6 ppm from wet weight inside *Amphimedon* sp.) and of course manzamines. Finally, manzamines could provide manadomanzamine A[19] **1.041** (24 ppm from wet weight inside *Acanthostrongylophora* sp.), ma'eganedin A[20] **1.042** (9 ppm from wet weight inside *Amphimedon* sp.), acantholactam[11] **1.043** (15 ppm

[15] Kong, F.; Andersen, R. J. *Tetrahedron* **1995**, *51*, 2895.
[16] Jaspars, M.; Pasupathy, V.; Crews, P. *J. Org. Chem.* **1994**, *59*, 3253.
[17] Kubota, T.; Kamijyo, Y.; Takahashi-Nakaguchi, A.; Fromont, J.; Gonoi, T.; Kobayashi, J. *Org. Lett.* **2013**, *15*, 610.
[18] Kobayashi, J.; Watanabe, D.; Kawasaki, N.; Tsuda, M. *J. Org. Chem.* **1997**, *62*, 9236.
[19] Peng, J.; Hu, J-F.; Kazi, A. B.; Li, Z.; Avery, M.; Peraud, O.; Hill, R. T.; Franzblau, S. G.; Zhang, F.; Schinazi, R. F.; Wirtz, S. S.; Tharnish, P.; Kelly, M.; Wahyuono, S.; Hamann, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 13382.
[20] Tsuda, M.; Watanabe, D.; Kobayashi, J. *Tetrahedron Lett.* **1998**, *39*, 1207.

from wet weight inside *Acanthostrongylophora* sp.), zamamidine B[21] **1.044** (6 ppm from wet weight inside *Amphimedon* sp.) and the previous reported kauluamine **1.021** and *neo*-kauluamine **1.022** (Scheme 15).



Scheme 15: manzamine family

[21] Takahashi, Y.; Kubota, T.; Fromont, J.; Kobayashi, J. *Org. Lett.* **2009**, *11*, 21.

3. Bioactivities

Nearly thirty years ago, Sakai and Higa tested these new alkaloids against P388 mouse leukemia cells.[1,2] Manzamine A **1.001**, B **1.002**, and C **1.003** exhibited IC_{50} values of 0.07 µg/ml, 6 µg/ml and 3 µg/ml, respectively, revealing the fact that even with a simpler structure, manzamine C **1.003** is more active than manzamine B **1.002**.

Since that day, the manzamine family was proven to exhibit activities against *Staphylococcus aureus*[3,17], carcinoma cells[5,8,14], was furthermore antibacterial[18,22] and insecticidal[23]. Finally, they display antiparasitic activities with some of the greatest potential for possible clinical applications existing for malaria and *Mycobacterium tuberculosis*.[19,24]

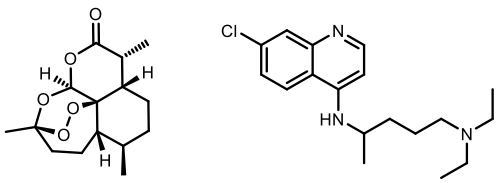
In 2000, Kara *et al.* performed *in vivo* antimalarial experiments. The survival over time of mice infected with *Plasmodium berghei* was compared to survival after treatment with a single intraperitoneal injection of 100 µmol/kg of either manzamine A **1.001**, manzamine G **1.015**, manzamine F **1.008**, artemisinin **1.045** and chloroquine **1.046**. A single intraperitoneal administration of manzamine A **1.001** or manzamine G **1.015** prolonged the survival of *P. berghei*-infected mice for more than 10 days, with 40 % of mice treated, surviving for more than 60 days and recovering with no detectable parasitaemia. The ability of manzamine A **1.001** and G **1.015** to extend the

[22] Harrison, B.; Talapatra, S.; Lobkovsky, E.; Clardy, J.; Crews, P. *Tetrahedron Lett.* **1996**, *37*, 9151.
[23] Edrada, R. A.; Proksch, P.; Wray, V.; Witte, L.; Müller, W. E. G.; Van Soest, R. W. M. *J. Nat. Prod.* **1996**, *59*, 1056.
[24] (a) Ang, K. K. H.; Holmes, M. J.; Higa, T.; Hamann, M. T.; Kara, U. A. K. *Antimicrob. Agents Chemother.* **2000**, *44*, 1645. (b) El Sayed, K. A.; Kelly, M.; Kara, U. A. K.; Ang, K. K. H.; Katsuyama, I.; Dunbar, D. C.; Khan, A. A.; Hamann, M. T. *J. Am. Chem. Soc.* **2001**, *123*, 1804. (c) Rao, K. V.; Santarsiero, B. D.; Mesecar, A. D.; Schinazi, R. F.; Tekwani, B. L.; Hamann, M. T. *J. Nat. Prod.* **2003**, *66*, 823. (d) Rao, K. V.; Kasanah, N.; Wahyuono, S.; Tekwani, B. L.; Schinazi, R. F.; Hamann, M. T. *J. Nat. Prod.* **2004**, *67*, 1314. (e) Arai, M.; Sobou, M.; Vilchéze, C.; Baughn, A.; Hashizume, H.; Pruksakorn, P.; Ishida, S.; Matsumoto, M.; Jacobs J. W. R.; Kobayashi, M. *Bioorg. Med. Chem.* **2008**, *16*, 6732. (f) Ashok, P.; Lathiya, H.; Murugesan, S. *Eur. J. Med. Chem.* **2015**, *97*, 928. (g) Ashok, P.; Ganguly, S.; Murugesan, S. *Drug. Discov. Today* **2014**, *19*, 1781.

lives of infected mice far exceeded that of chloroquine **1.046** and artemisinin **1.045**, two of the most important human therapeutic antimalarial drugs. Manzamine A **1.001** was toxic to mice at 500 µmol/kg, but it showed more slowly acting toxicity than chloroquine **1.046**, which caused almost instantaneous death of the treated mice at 500 µmol/kg (Scheme 16) and (Table 1).

Treatment	No. of mice surviving on the following day after treatment							
	0	**2**	**4**	**6**	**10**	**15**	**25**	**60**
Manzamine A **1.001**	5	5	5	5	5	4	2	2
Manzamine G **1.015**	5	5	5	5	5	0		
Manzamine F **1.008**	5	5	0					
Artemisinin **1.045**	5	5	4	0				
Chloroquine **1.046**	5	5	5	5	0			
Control	14	14	0					

Table 1: Survival over time



Scheme 16: Artemisinin and chloroquine

Transmission electron microscopy revealed progressive changes in the morphology of *P. berghei* parasites after intraperitoneal administration of manzamine A **1.001**, with initial changes seen only one hour after treatment. One hour of exposure to manzamine A induced the formation of membrane-bound vesicles with various electron densities within some parasites. Four hours after treatment, other morphological changes, such as the development of electron-dense vesicles, were observed in more

parasites. By twelve hours after drug exposure, the parasite cytoplasm showed marked degeneration and was filled with electron-dense vesicles. Almost all parasites had degenerated by one day after exposure to manzamine A **1.001**.

In 2003 and 2004, Hamann *et al.* performed in vitro experiments against *Mycobacterium tuberculosis* and *Plasmodium falciparum* (W2 is the most highly resistant strains in *P. falciparum*). Most manzamines were active against *M. tuberculosis* with MICs < 12.5 µg/ml. The minimal difference in the *Mycobacterium tuberculosis* activity of manzamines A **1.001** and J **1.010** may indicate that the structure-activity relationship and targets for *M. tuberculosis* and malaria are significantly different (as reminder manzamines A **1.001** and J **1.010** only differ by a bond between N-27 and C-34 at the bottom). Comparison of manzamine E **1.007** and F **1.008** activities indicate that the hydroxyl functionality and its position on the β-carboline moiety may play a role in the biological activity. The significant activity of ircinol A **1.017** against *M. tuberculosis* suggested that the β-carboline moiety is not essential for activity (Table 2).

Compound	*M. tuberculosis* (H37Rv) MIC µg/ml	*P. falciparum* (D6 clone) IC 50 ng/ml	*P. falciparum* (W2 clone) IC 50 ng/ml
Manzamine A **1.001**	1.5	4.5	8.0
Manzamine E **1.007**	3.8	3400	4760
Manzamine F **1.008**	2.6	780	1700
Manzamine G **1.015**	0.9	6.0	8.0
Manzamine J **1.010**	1.7	1300	750
Manzamine X **1.019**	NT	950	2000
Ircinal A **1.011**	30.2	NA	NA
Ircinol A **1.017**	1.9	2400	3100
neo-kauluamine **1.022**	2.0	1700	2800
Rifampin	0.5	NT	NT
Artemisinin **1.045**	NT	10	6.3
Chloroquine **1.046**	NT	15.5	170

NA = not active (centration 5.0 µg/ml); NT = not tested

Table 2: Activity against tuberculosis and malaria

Chapter II

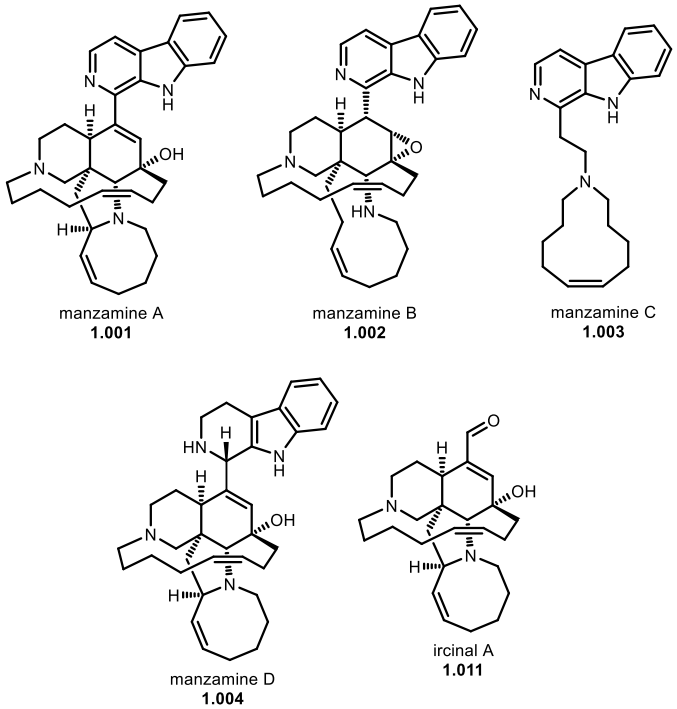
Previous Syntheses of Manzamines

Since their discovery, manzamines have been a target of synthetic interest for many groups around the world. Despite these joined efforts, only three manzamines have been synthesized to date; manzamine A **1.001**, manzamine C **1.003** and manzamine D **1.004** (Scheme 1). Most of the pathways for manzamine A synthesis were channelled through the production of ircinal A **1.011** and manzamine D **1.004**:

- Manzamine A **1.001**:
    - In 1998 by Jeffrey D. Winkler[1]
    - In 2002 by Stephen F. Martin[2]
    - In 2010 by Tohru Fukuyama[3]
    - In 2012 by Darren J. Dixon[4]
- Manzamine C **1.003**:
    - In 1991 by Tohru Hino[5]
    - In 1992 by Hans Gerlach[6]
    - In 2000 by Ellen J. Beck[7]

[1] Winkler, J. D.; Axten, J. M. *J. Am. Chem. Soc.* **1998**, *120*, 6425.
[2] (a) Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866. (b) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Yue-Ling, W.; Chen, H-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584.
[3] Toma, T.; Kita, Y.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 10233.
[4] Jakubec, P.; Hawkins, A.; Felzmann, W.; Dixon, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 17482.
[5] (a) Torisawa, Y.; Hashimoto, A.; Nakagawa, M.; Hino, T. *Tetrahedron Lett.* **1989**, *30*, 6549. (b) Torisawa, T.; Hashimoto, A.; Nakagawa, M.; Seki, H.; Hara, R.; Hino, T. *Tetrahedron* **1991**, *47*, 8067.
[6] Nowak, W.; Gerlach, H. *Liebigs Ann. Chem*. **1993**, 153.
[7] MaGee, D. I.; Beck, E. J. *Can. J. Chem*. **2000**, *78*, 1060.

Unfortunately, manzamine B **1.002** has not been synthetized to date. Its scaffold can be considered as more challenging than most of the manzaminoids due to two macrocycles and a central cyclohexane carrying six stereogenic centres. Its bioactivities are similar to manzamine C **1.003** (*Cf.* Chap I) (Scheme 1).

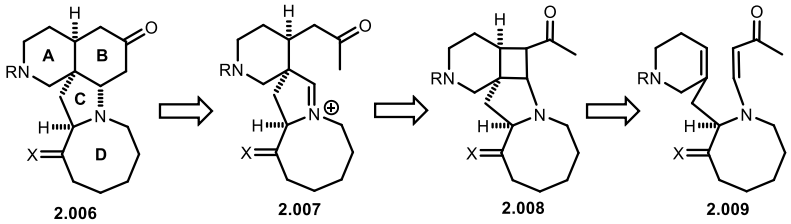


Scheme 1: Manzamines A, B, C, D and ircinal A

In this chapter we will have an overview of the total syntheses of manzamine A **1.001** and their applied methodologies according to chronological order.

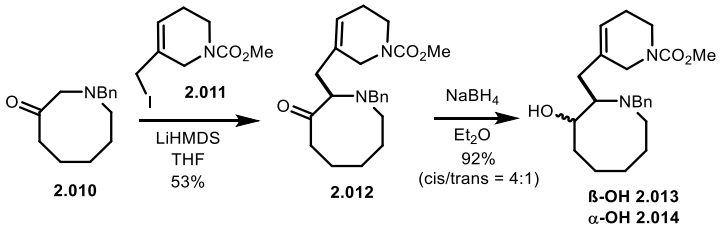
1. Manzamine A in 1998 by Winkler

The authors planned to use a [2+2] photochemical reaction as key step to reach the ABCD scaffold.[8] The target molecule **2.006** could come from **2.007** upon enol addition on iminium. Ketone-iminium **2.007** is a rearranged product of cyclobutene **2.008** which derived from **2.009** under specific light condition. This closure cascade is called an Intramolecular Vinylogous Amide PHotocycloAddition/Retro-Mannich fragmentation/Mannich closure Cascade and will be noted "pharM". In this sequence, only one stereogenic centre is required in order to direct all the other chiral centres within the central core ABCD (Scheme 2).[9]



Scheme 2: Winkler's retrosynthesis

The synthesis of the photosubstrate started with the alkylation of azocinone **2.010** with allylic iodide **2.011** and proceeded to afford ketone **2.012** in 53 % yield. A separable mixture (4:1) of *cis* **2.013** and *trans* **2.014** alcohols was obtained after sodium borohydride reduction (Scheme 3).

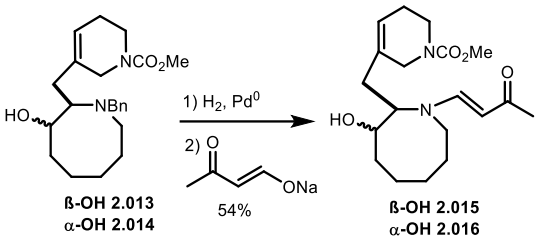


Scheme 3: Synthesis of 2.013 and 2.014

[8] (a) Winkler, J. D.; Siegel, M. G.; Stelmach, J. E. *Tetrahedron Lett*. **1993**, *34*, 6509. (b) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003.

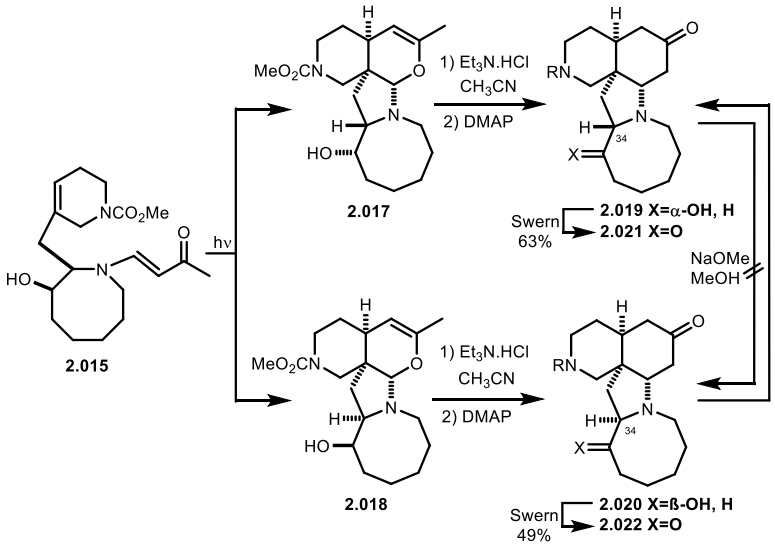
[9] Winkler, J. D.; Stelmach, J. E.; Siegle, M. G.; Haddad, N.; Axten, J. Dailey, W. P. III *Isr. J. Chem.* **1997**, *37*, 47.

The two amines were debenzylated and condensed with sodium-formyl-acetone to give **2.015** and **2.016** in 54 % yield over two steps (Scheme 4).



Scheme 4: Photo-precursors 2.015 and 2.016

Irradiation of *cis*-**2.015** led to the formation of the aminals **2.017** and **2.018** in a 2:1 ratio. Exposure of the mixture to triethylamine hydrochloride in acetonitrile, followed by the action of DMAP at reflux induced the formation of ketoalcohols **2.019** and **2.020** in 50 % overall yield from **2.015** (Scheme 5).

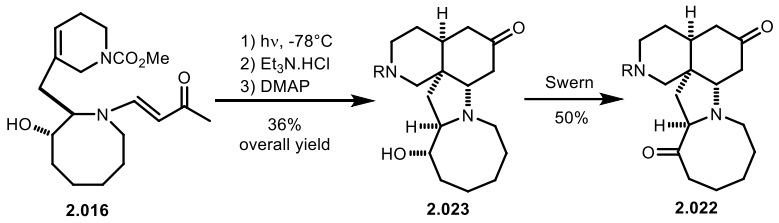


Scheme 5: PharM sequence on 2.015

The stereochemical assignments were made by X-ray analysis of the diketone **2.021** obtained through Swern oxidation of **2.019**. As the authors observed the diketone **2.021** has a relative stereochemistry at C34 epimeric

to that of manzamine A **1.001,** whereas the diketone **2.022** possesses all the correct stereogenic centres. Equilibration studies with sodium methoxide in methanol revealed that diketone **2.022** could be converted in diketone **2.021** while the transformation from **2.021** to **2.022** was not observed. This information tends to prove **2.021** as the more stable of both tetracycles (Scheme 5).

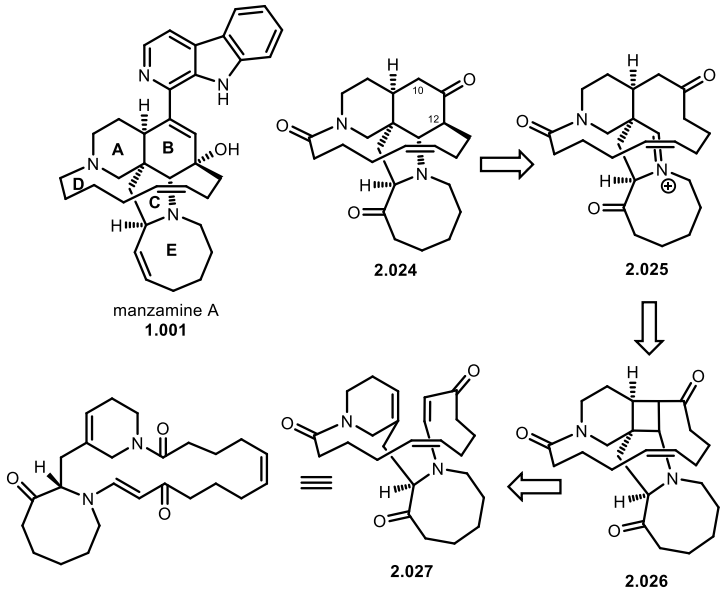
Irradiation of the *trans* alcohol **2.016** at -78°C followed by retro-Mannich fragmentation and Mannich closure led to **2.023** as single diastereomer in 36 % yield. This material can be converted into the diketone **2.022** *via* Swern oxidation (Scheme 6).



Scheme 6: PharM sequence on 2.016

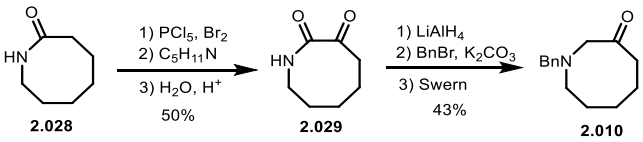
These preliminary results established that intramolecular vinylogous amide photocycloaddition using an eight-membered ring template efficiently forge the tetracyclic ring system of manzamine A **1.001**.

A new retrosynthetic analysis was proposed with PharM sequence, this time for the construction of ABCDE pentacycle. Once again, only one stereogenic centre in the starting material was planned to guide the installation of all other stereocentres in the scaffold. The diketone amide **2.024** should be a suitable precursor for the incorporation of the C10 β-carboline and the C12 tertiary hydroxyl. The pentacycle **2.024** could be derived from Mannich closure of the keto-iminium **2.025**, which could result from the retro-Mannich fragmentation of **2.026**. The cyclobutane **2.026** could come from the [2+2] photoaddition of macrocyclic vinylogous amide **2.027**. This disconnection represents an efficient concept as the ADE moiety is converted in one-pot into the ABCDE pentacycle of manzamine (Scheme 7).



Scheme 7: New retrosynthesis

The previous pathways for the synthesis of azocinone **2.010** was modified for a larger scale synthesis. A three-step dibromation, bromide-elimination and hydrolysis sequence starting from commercially available caprolactam **2.028** allowed access to keto-lactam **2.029**.[10] Finally, **2.029** was reduced with lithium aluminium hydride, alkylated and oxidized to the desired azocinone **2.010** (Scheme 8).

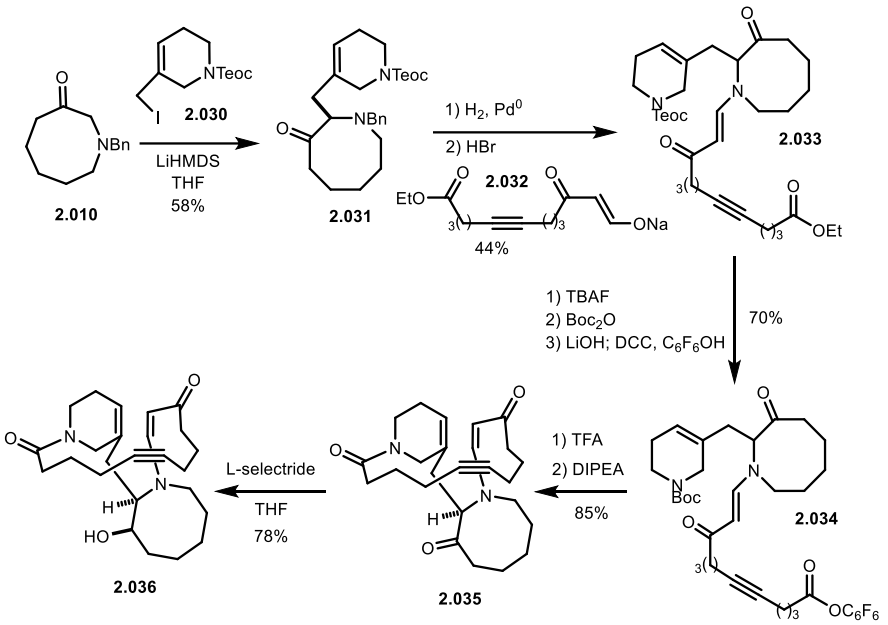


Scheme 8: Azocine synthesis

The azocinone **2.010** was C-alkylated with vinyl iodide **2.030** bringing forth the bicycle AE **2.031**. This intermediate was then debenzylated and coupled with **2.032** to produce the vinyl amide **2.033**. The introduced side chain is capped with an ester at its terminus. The reason for this is that the ensuing macrocyclization should occur more easily through macro-

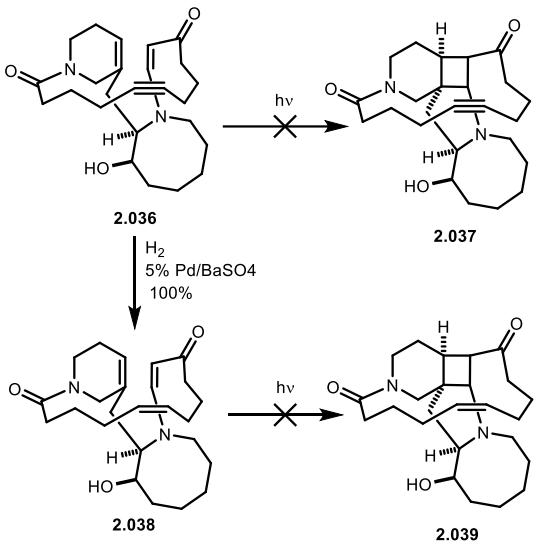
[10] Brouillette, W. J.; Einspahr, H. M. *J. Org. Chem.* **1984**, *49*, 5113.

lactamization than macro-alkylation. The additional presence of an acetylene further decreases conformational freedom, thereby making the cyclization entropically less demanding. The removal of Teoc function, reprotection with Boc anhydride and activation of the ester afforded **2.034**. The macrocyclization materialized in a very good yield furnishing **2.035** in 85 % over two steps. The photochemical reaction with similar substrate as **2.035** led to mixtures of undesired products. To preclude it, the ketone was reduced with L-selectride affording the *cis*-alcohol **2.036** (Scheme 9).



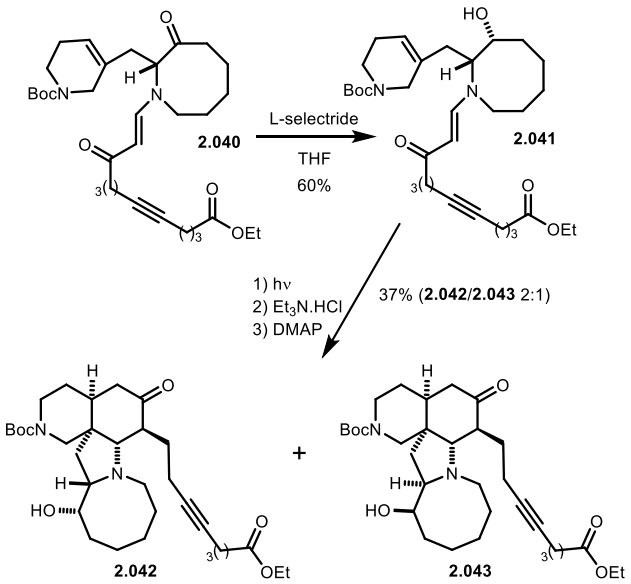
Scheme 9: Synthesis of photo-precursor 2.036

Instead of undergoing the planned pharM sequence, alcohol **2.036** does not lead to product **2.037** but to a complex mixture of products containing multiple olefinic moieties. Alternatively, **2.038** was made through Lindlar reduction of **2.036**. Unfortunately, the pharM sequence did not produce the cyclobutane scaffold **2.039** (Scheme 10).



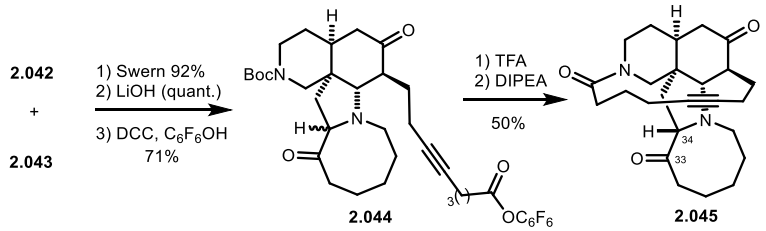
Scheme 10: Tests of PharM sequence

The failure of the macrocyclic vinylogous amide photosubstrates to undergo the desired transannular photocycloaddition led the authors to examine an alternative strategy (Scheme 11). In this modified pathway, ketone **2.040** was reduced with L-selectride to the *cis*-alcohol **2.041**, followed by the pharM sequence to achieve the tetracycles **2.042** and **2.043** in a 2:1 ratio.



Scheme 11: New route

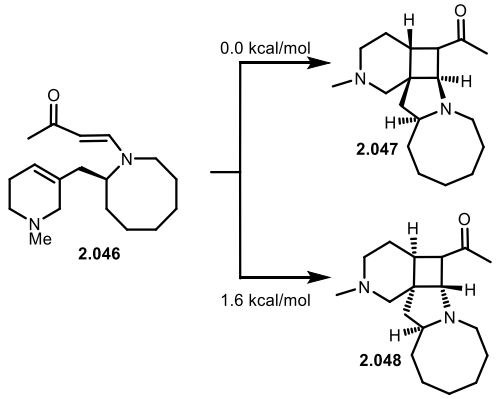
The epimeric mixture of tetracycles **2.042** and **2.043** was oxidized and activated to acquire the ester **2.044**. The macrocyclization occurred in two steps with trifluoro acetic acid and diisopropylethylamine in a 50 % yield. The mixture led to a single product in a stereoconvergent fashion, as explained earlier in this chapter (Scheme 12).



Scheme 12: Macrocyclization

The pharM sequence was able to forge the pentacycle ABCDE of manzamine A **1.001**. However, to finish the synthesis, few issues need to be fixed such as the presence of the incorrect epimer at C34, some functional group transformations and the incorporation of the β-carboline moiety.

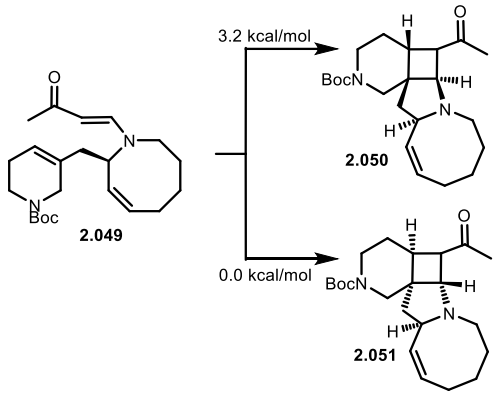
At this point of the synthesis, Winkler *et al.* performed conformational calculations to optimize their pathway.[11] The ground state conformations involved in the cycloadditions of **2.046** and **2.049** were analyzed. The computational data showed an energy difference of 1.6 kcal/mol between the lowest energy conformers leading to **2.047** and **2.048**, thereby favouring the formation of **2.047**. Therefore, in this system, the vinylogous amide is located in the same plane as the nitrogen and the tertiary carbon of the eight-membered ring. The [2+2] cycloaddition takes place on the top face of the vinylogous amide to give the adduct **2.047**, hence producing the incorrect relative stereochemistry for the synthesis of manzamines (Scheme 13).



Scheme 13: Energetic pathways for 2.046 in PharM sequence

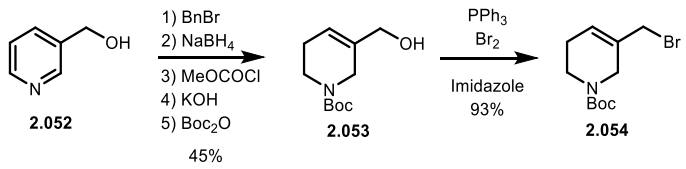
Owing to the unsaturated azocine system in **2.049**, the conformation of the eight-membered ring will be different. The calculations show an energy difference of 3.2 kcal/mol between the lowest energy transition structures leading to **2.050** and **2.051**, favouring the formation of the product **2.051**. The unsaturation in the eight-membered ring creates a torsional strain affecting a conformational change that places the enone moiety orthogonal to the ring plane (Scheme 14).

[11] Winkler, J. D.; Axten, J.; Hammach, A. H.; Kwak, Y-S.; Lengweiler, U.; Lucero, M.; Houk, K. N. *Tetrahedron* **1998**, *54*, 7045.



Scheme 14: Energetic pathways for 2.049 in PharM sequence

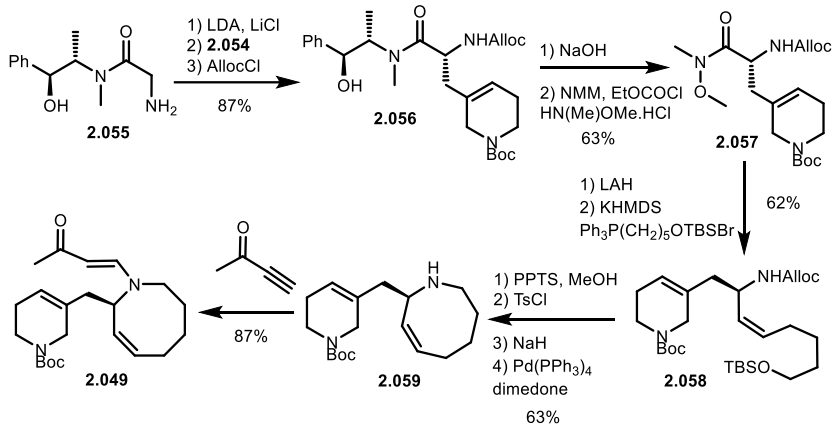
To shed light on the veracity of their calculations, the synthesis of **2.049** was started with the alcohol **2.052**. At first it underwent benzylation, then reduction of the pyridinium salt with $NaBH_4$ and purification through a protection-deprotection-protection process afforded **2.053**. Finally, the alcohol was converted to the vinylic bromide **2.054** (Scheme 15).



Scheme 15: Synthesis of 2.054

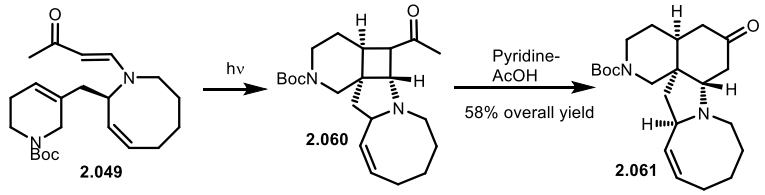
Myers pseudoephedrine alkylation was used to control the absolute stereochemistry of **2.056**.[12] Pseudoephedrine was exchanged for Weinreb amide **2.057**, followed by reduction and Wittig reaction to afford **2.058**. Deprotection, activation and macrocyclization in the conditions described by Nakagawa *et al.*[13] led to the eight-membered ring **2.059** after deprotection of the Alloc function. Conjugate addition to butynone gave the product **2.049** which went through the calculations (Scheme 16).

[12] Myers, A.; Gleason, J.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488.
[13] Torisawa, Y.; Motohashi, Y.; Ma, J.; Hino, T.; Nakagawa, M. *Tetrahedron Lett.* **1995**, *36*, 5579.



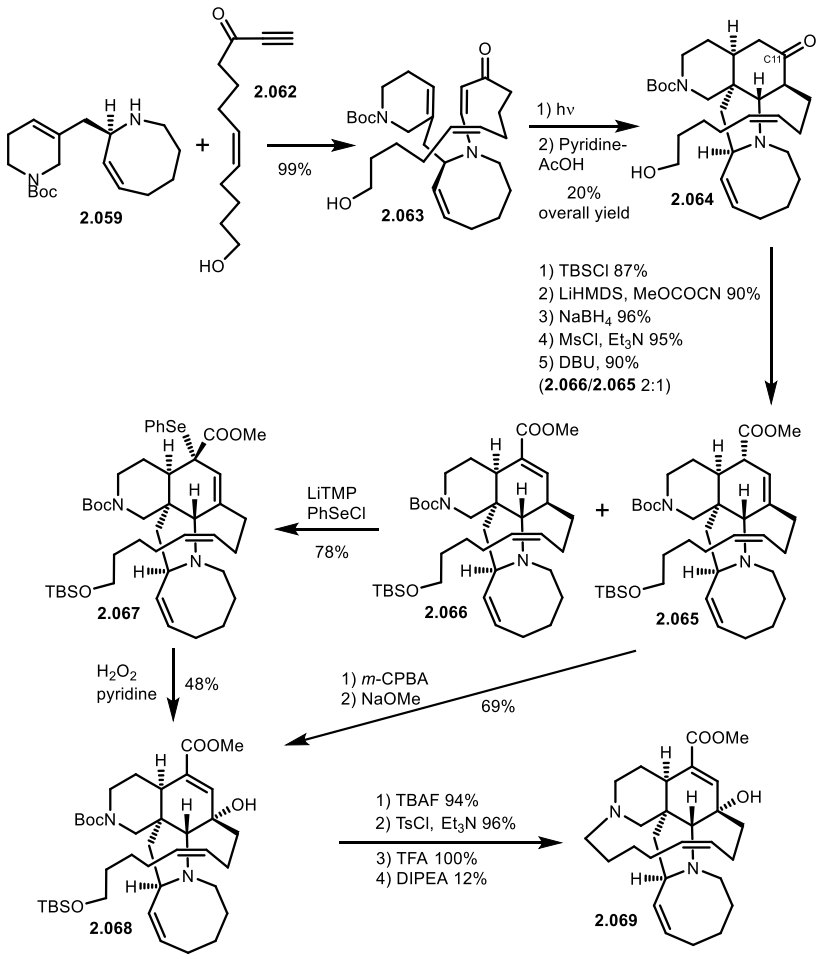
Scheme 16: Enantioselective synthesis of 2.049

The pharM sequence was successfully tested on substrate **2.049** which provided the desired tetracycle **2.061** in a 58 % yield (Scheme 17).



Scheme 17: Successful test of PharM sequence

In order to disclose the endgame of the synthesis, azocine **2.059** was reacted with ynone **2.062** to bring forth the vinylogous amide **2.063** as precursor for the pharM sequence. Tetracycle **2.064** was obtained in 20 % and underwent the modification of the ketone C11 to the βγ unsaturated ester **2.065** and αβ unsaturated ester **2.066**, in a 1:2 ratio, respectively. Selenation of **2.066** produced **2.067** which eliminated under oxidative conditions leading to γ-hydroxy-αβ-unsaturated ester **2.068**. Epoxidation of **2.065**, followed by basic conditions provided the desired ester **2.068**. The macrocyclization sequence consisted in a deprotection-activation-deprotection-cyclization but met with very poor yield (12 %) in the cyclization step towards **2.069**. To improve this yield, the use of acetylene derivatives was envisioned as mentioned earlier (Scheme 18).

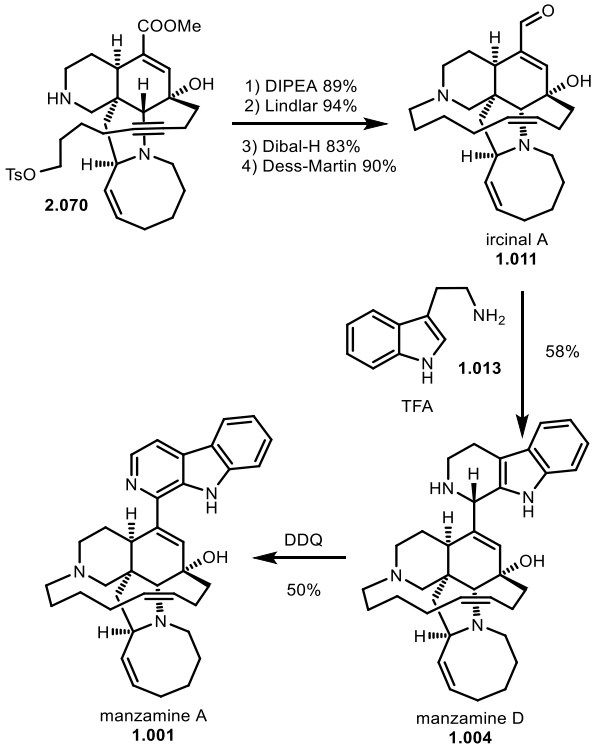


Scheme 18: Synthesis of pentacycle 2.069

The synthesis continued with **2.070** and a successful macrocyclization in 89 % yield, followed by reduction of the triple bond, reduction of the ester, and oxidation to the aldehyde to afford for the first time ircinal A **1.011** by synthesis. As described in the Kobayashi procedure[14], ircinal A **1.011** was converted into manzamine D **1.004** *via* action of

[14] Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.

tryptamine **1.013**. Final oxidation by DDQ led to manzamine A **1.001** (Scheme 19).

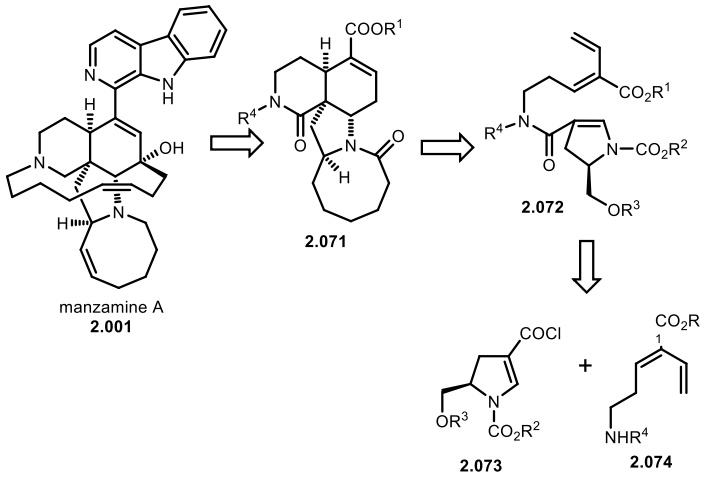


Scheme 19: Final steps of first manzamine synthesis

This concluded the first total synthesis of Ircinal A **1.011**, manzamine D **1.004** and manzamine A **1.001** after more than 10 years of investigation by Winkler group.

2. Manzamine A in 2002 by Martin

The retrosynthetic pathway proposed by Martin *et al.* suggested the use of an intramolecular Diels-Alder reaction to implement the central core **2.071** starting from diene **2.074** and dienophile **2.073** (Scheme 20).

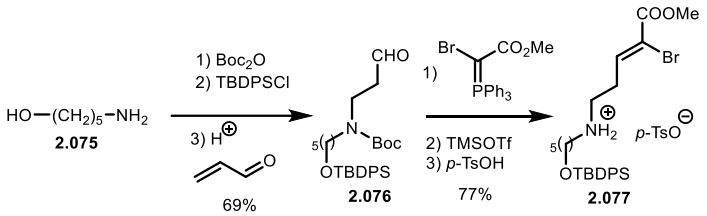


Scheme 20: Martin's retrosynthesis

During early investigations, the viability of several key aspects of this strategy were established, in particular, the intramolecular [4+2] cycloaddition using the vinylogous imide. Unfortunately, at this stage the subunit prepared was not ideally endowed for transformation into manzamine A **1.001**.[15]

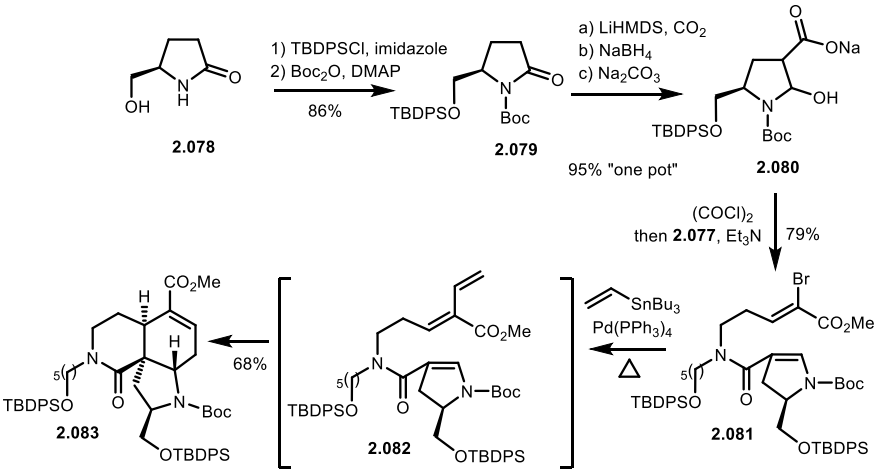
The synthesis commenced with the preparation of the diene precursor **2.077**. The commercially available amino-alcohol **2.075** was protected and reacted with acrolein producing the aldehyde **2.076**. Wittig olefination and deprotection followed by ammonium salt precipitation afforded **2.077** as a stable solid in 77 % yield (Scheme 21).

[15] (a) Martin, S. F.; Liao, Y.; Wong, Y.; Rein, T. *Tetrahedron Lett.* **1994**, *35*, 691. (b) Martin, S. F.; Chen, H. J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251.



Scheme 21: Synthesis of 2.077

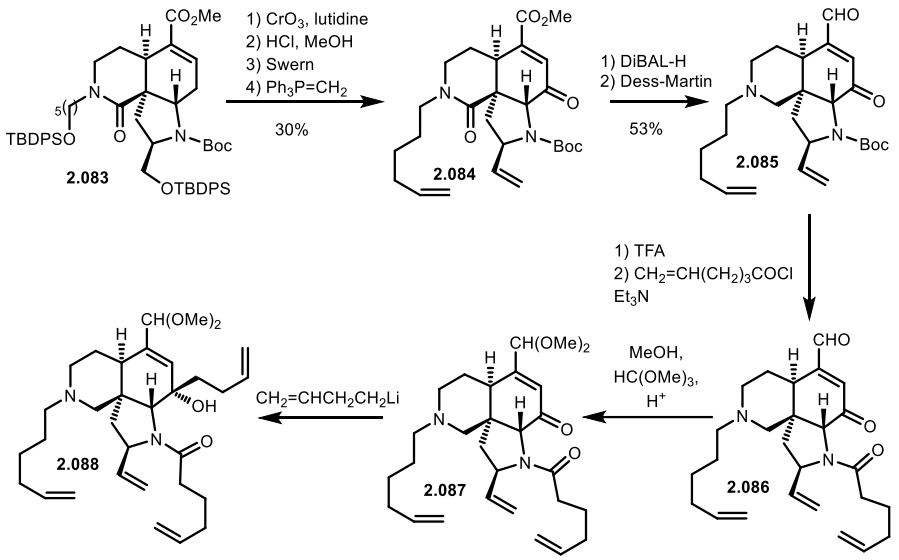
The synthesis of the dienophile precursor started with the commercially available pyrrolidinone **2.078**, which was protected in a two-step process to **2.079**. A "one-pot" procedure involving carbon dioxide, reduction and deprotonation provided **2.080** as a stable sodium carboxylate salt. These two reagents **2.080** and **2.077** subsequently underwent an amide-coupling reaction allowing access to the bromo-diene **2.081** in a nice 79 % yield. At this stage, the critical domino Stille/Diels-Alder reaction took place. In this event, **2.081** reacted with vinyl tributylstanne in the presence of Pd(0) to afford the triene **2.082** that spontaneously cyclized *via* an intramolecular Diels-Alder reaction to give solely **2.083** in a 68 % overall yield. In this sequence, the single stereocentre of **2.081** defined the absolute and relative stereochemistry of all the other chiral centres in **2.083** (Scheme 22).



Scheme 22: Synthesis of tricyclic compound 2.083

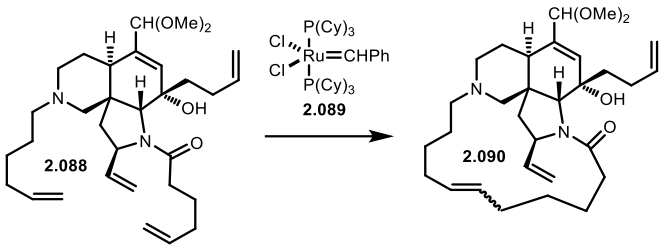
In the next phase of the synthesis, the 13 and 8 membered rings were installed by ring closing metathesis (RCM). Compound **2.083** was submitted

to a chromium induced allylic oxidation, a double TBDPS deprotection, directly followed by a Swern oxidation and a Wittig reaction, eventually leading to **2.084** in a 30 % yield. The ester **2.084** was reduced to the corresponding alcohol and oxidized back to aldehyde **2.085** by Dess-Martin periodinane. The N-Boc protecting group **2.085** was exchanged for an amide **2.086**. The aldehyde **2.086** was protected as the acetal **2.087** and the ketone was selectively alkylated to provide the polyene adduct **2.088** (Scheme 23).



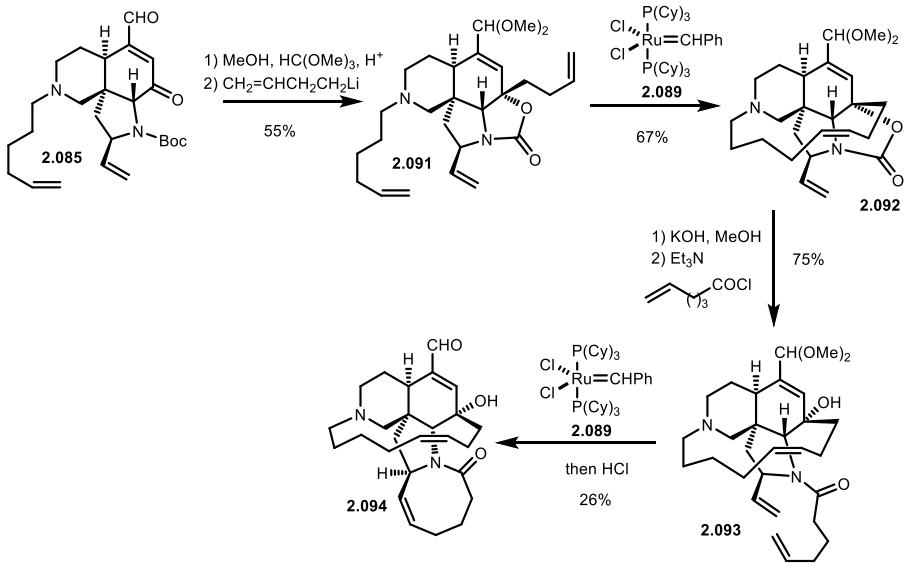
Scheme 23: Synthesis of tetraene 2.088

The following extremely ambitious step was to forge both the 13 and 8 membered rings using the Grubbs' catalyst **2.089**. Unfortunately, no detectable amounts of the desired pentacyclic skeleton of protected ircinal A were delivered. Rather, an inseparable mixture was isolated that contained two compounds identified as the isomeric tetracyclic olefins **2.090** (Scheme 24).



Scheme 24: Grubbs' cyclization of polyene 2.088

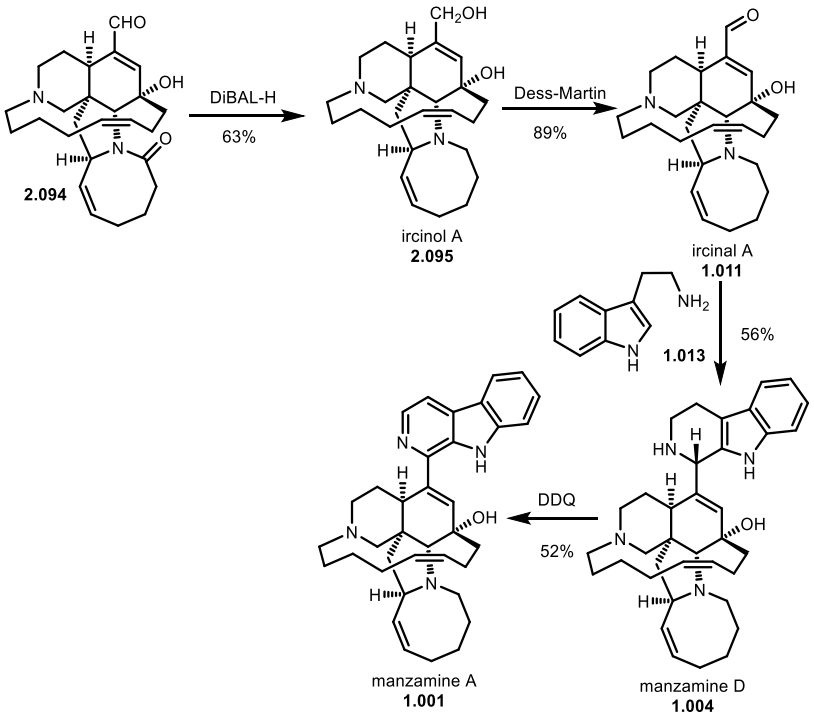
Instead of bis-macrocyclization, Martin *et al.* went back to a safer process. Protection and alkylation of **2.085** into **2.091** followed by the first RCM afforded **2.092** in a 67 % yield. Deprotection of the cyclic carbamate **2.092** was carried out using potassium hydroxide in methanol and directly converting the amine into the amide **2.093**. The second RCM was performed with the same Grubbs' catalyst and the final mixture was quenched with acidic water furnishing the amide of ircinal A **2.094** in 26 % yield (Scheme 25).



Scheme 25: Synthesis of ircinal A amide 2.094

The reduction of **2.094** with DiBAL-H gave Ircinol A **2.095**, which was oxidized with Dess-Martin periodinane to deliver synthetic Ircinal A in 89 %

yield. Then once again, Kobayashi's method[16] was utilized to bring forth manzamine A **1.001** (Scheme 26).

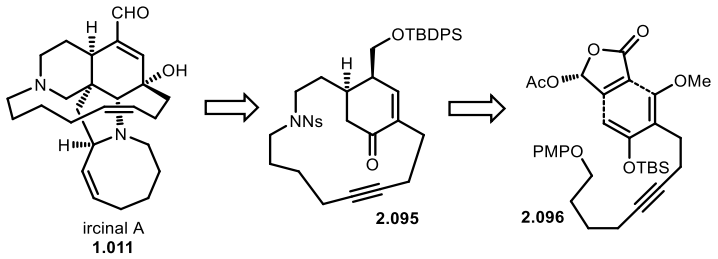


Scheme 26: Manzamine A 1.001 synthesis

[16] Kondo, K.; Shigemori, H.; Kikuchi, Y.; Ishibashi, M.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 2480.

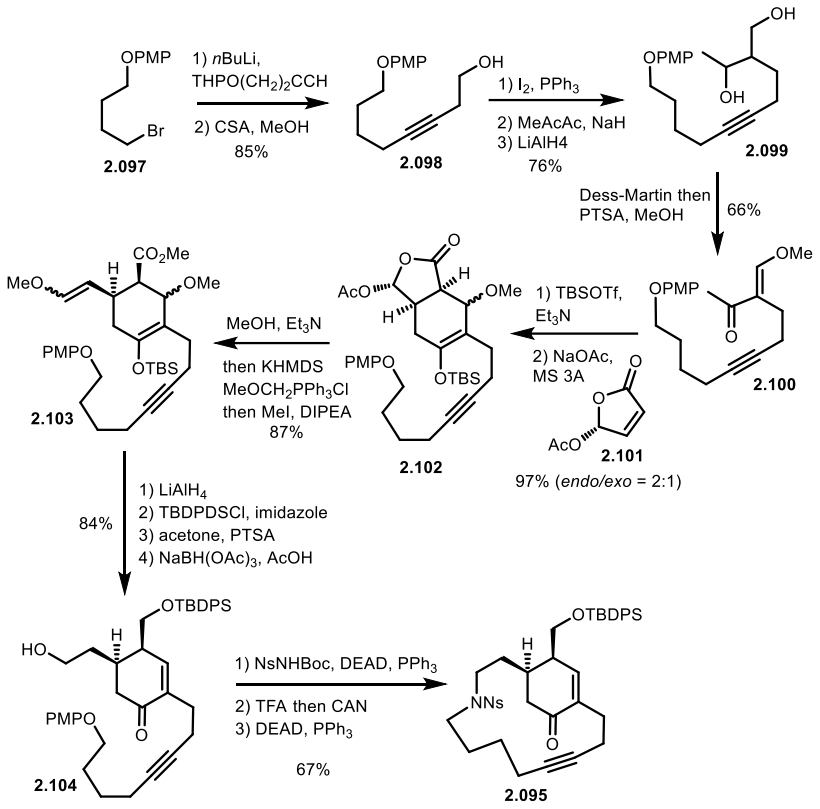
3. Manzamine A in 2010 by Fukuyama

The retrosynthetic analysis proposed by Fukuyama *et al.* envisioned that the bicyclic ketone **2.095** would be ideal for controlling the stereochemistry of all the stereogenic centres of ircinal A **1.011**. This ketone could come from a Diels-Alder reaction, as proposed for **2.096** (Scheme 27).



Scheme 27: Fukuyama retrosynthetic pathway

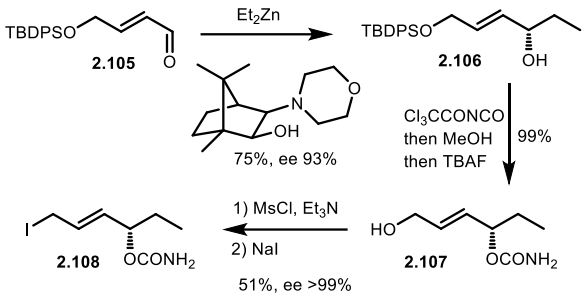
Execution of the above strategy required the preparation of vinylogous ester **2.100**. Starting from alcohol **2.097** which was turned into **2.098** through nucleophilic substitution and a deprotection. Alcohol **2.098** underwent activation, an alkylation with methyl acetoacetate and finally, reduction with lithium aluminium hydride to afford diol **2.099** in 76 % yield. Diol **2.099** was oxidized and protected to vinylogous ester **2.100** which was converted into vinyl-enolate and directly used for Diels-Alder reaction with **2.101** to afford bicyclic **2.102**. The use of sodium acetate and molecular sieves drastically improved the conversion, as they were proven to block hydrolysis of enolate in **2.096**. The Diels-Alder adduct **2.102** was modified in an opening-Wittig-methylation one-pot process to furnish **2.103**. Reduction of the methyl ester and protection of the obtained alcohol was followed by deprotection of the methyl-enol and its reduction to alcohol **2.104** in the presence of an enone. Mitsunobu reaction was carried out to convert the alcohol into a nosylamide function, followed by double deprotection, and then Mitsunobu reaction once again to create macrocycle **2.095** (Scheme 28).



Scheme 28: Synthesis of macrocycle 2.095

The next challenge was the creation of the quaternary stereogenic centre. Allyl iodide **2.108** was chosen as a key electrophile for accessing the substrate for the sigmatropic rearrangement. Enantioselective addition of diethylzinc[17] to aldehyde afforded the desired alcohol **2.106** in 93 % ee. Introduction of a carbamate group and then deprotection and iodination of the primary alcohol followed by recrystallisation afforded enantiomerically pure iodide **2.108** (Scheme 29).

[17] Nugent, W. A. *Chem. Commun.* **1999**, 1369.

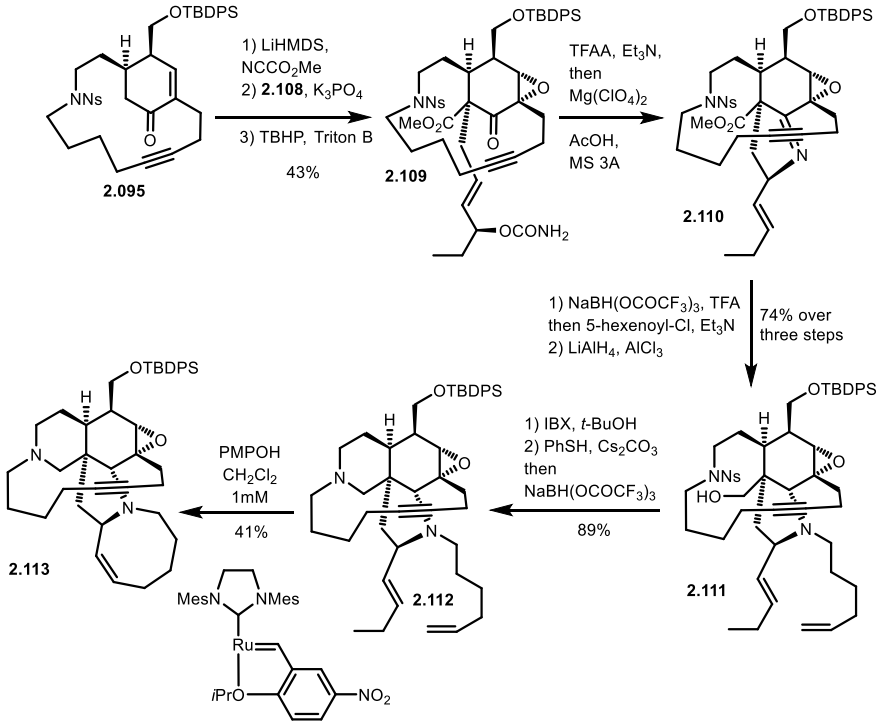


Scheme 29: Synthesis of enantiomerically pure allyl iodide 2.108

Following Mander's protocol[18] ketone **2.095** was converted into β-ketoester, which was subjected to allylation with **2.108**. As expected, stereoselective alkylation occurred from the sterically less crowded α-face to give a single product. Similarly, treatment with TBHP and Triton B afforded epoxyketone **2.109** as a single diastereomer. Upon dehydration of **2.109** with trifluoroacetic anhydride and triethylamine, the critical [3,3]-sigmatropic rearrangement proceeded even at 0°C to give the corresponding isocyanate with complete control of stereochemistry. The resulting isocyanate had to be converted into imine **2.110** under anhydrous conditions because **2.110** was susceptible to hydrolysis even under neutral conditions, triggering irreversible lactamization with the methyl ester. After extensive experimentation, the authors found that treatment of the isocyanate with acetic acid and magnesium perchlorate in the presence of molecular sieves enabled the desired transformation into **2.110**. Subsequent reduction of imine **2.110** and acylation with 5-hexenoyl chloride afford the amide-ester which was reduced to alcohol **2.111** using lithium aluminium hydride and aluminium trichloride. At this stage, the ring-closing metathesis for construction of the azocine ring was attempted. Unfortunately, because of the rapid isomerization of the terminal alkene, the ring-closing metathesis afforded a significant amount of the undesired seven-membered ring. Thus, the decision to create first the piperidine ring was obvious. IBX oxidation of **2.111** in *tert*-butyl alcohol, removal of the nosyl group and reduction of the resultant hemiaminal afforded diamine **2.112**. The last crucial step of the synthesis was the ring-closing metathesis of diamine **2.112**. Although

[18] Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

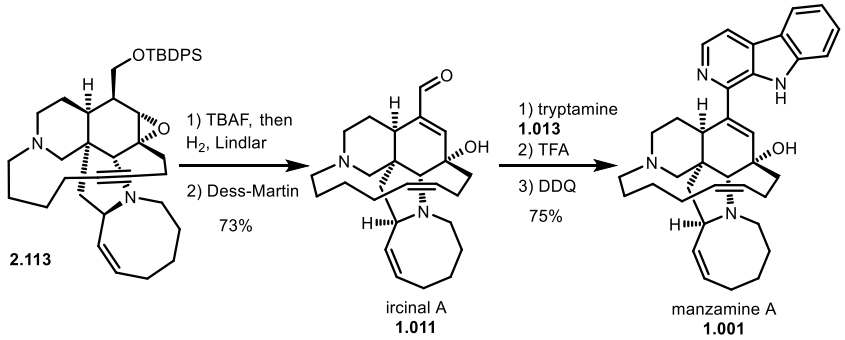
isomerization of the terminal alkene was not observed, participation of the tertiary amines and the alkyne were the major problems. After extensive efforts, reproducible results were obtained when a Hoveyda-Grubbs modified catalyst was used to afford pentacycle **2.113** (Scheme 30).



Scheme 30: Synthesis of pentacycle 2.113

Deprotection of the TBDPS ether, reduction of the triple bond and Dess-Martin oxidation lead to ircinal A **1.011**. Ircinal A was converted to manzamine A **1.001** through a modified procedure. During the investigation of the Pictet-Spengler reaction, they found that condensation of **1.011** with tryptamine **1.013** and subsequent cyclization required completely different acidic conditions. An efficient conversion of ircinal A **1.011** to manzamine D **1.004** was achieved when these reactions were conducted separately. Subsequent DDQ oxidation was hampered by incomplete conversion, which could eventually be solved by the use of DDQ recrystallized from

dichloromethane. Manzamine A **1.001** was thus obtained in 75 % overall yield (Scheme 31)**.**

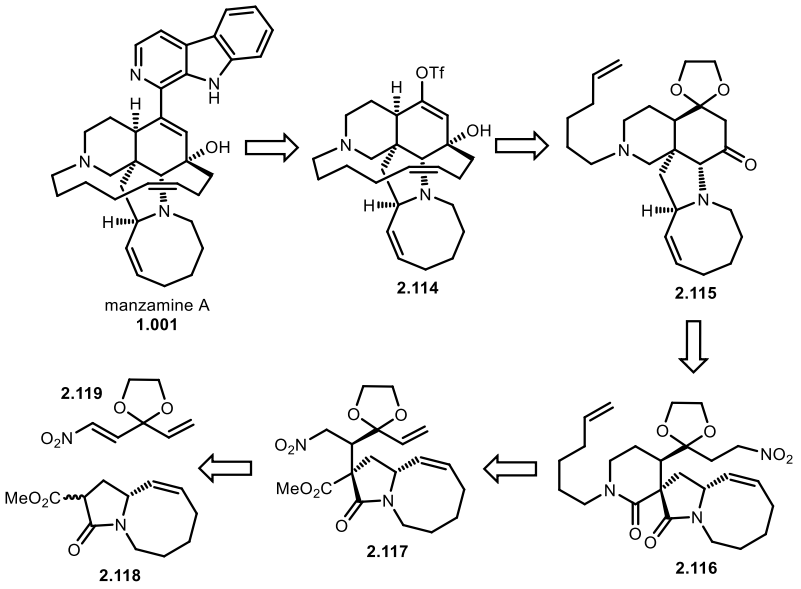


Scheme 31: Synthesis of manzamine A 1.001

4. Manzamine A in 2012 by Dixon

In their retrosynthetic pathway, Dixon *et al.* identified enol triflate **2.114** as valuable late-stage intermediate, allowing access to manzamine A **1.001**, but also other family members such as ircinol A **2.095** and ircinal A **1.011**.

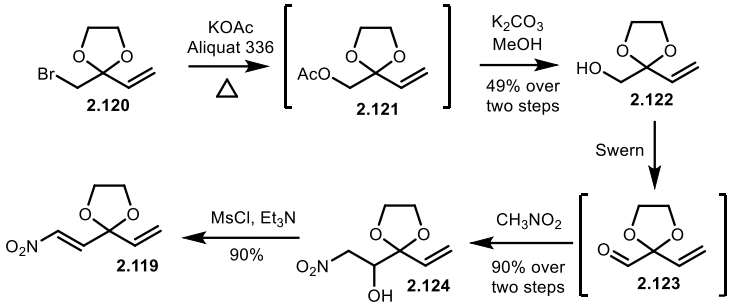
A short route initiated by stereoselective Michael addition of **2.118** to the nitro olefin **2.119**. The nitro-ester adduct **2.117** would be primed for annulation *via* nitro-Mannich/lactamization cascade to **2.116**. The nitro function in **2.116** would play a dual role allowing an intramolecular Mannich type reaction and a subsequent oxidation *via* Nef reaction to cyclohexanone **2.115**. Finally, a stereoselective addition alkylation to the resulting carbonyl group followed by enol triflate formation and RCM, would provide the key late-stage intermediate **2.114** (Scheme 32).



Scheme 32: Dixon's retrosynthesis

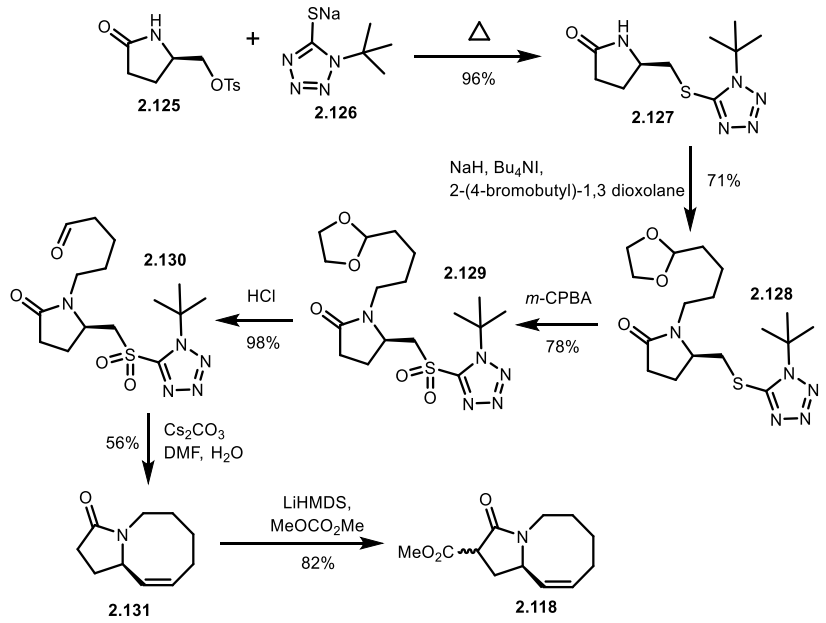
The synthesis started with the preparation of the Michael addition partners **2.118** and **2.119**. Nucleophilic substitution of **2.120** was nontrivial but achieved with potassium acetate and Aliquat 336 at 120°C, to provide

2.121 as intermediate which underwent smooth methanolysis to alcohol **2.122** in a very decent yield of 49 %. Swern oxidation occurred without incident and the crude aldehyde **2.123** reacted with nitromethane giving the Henry adduct **2.124**. Condensation of **2.124** with the first partner **2.119** took place with methanesulfonyl chloride and triethylamine (Scheme 33).



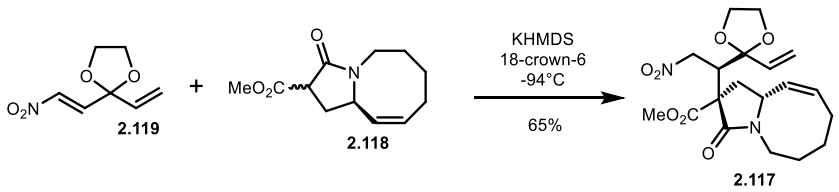
Scheme 33: Synthesis of first partner 2.119

The second partner **2.118** was constructed with the tosylate of pyroglutaminol **2.125** which underwent a nucleophilic substitution with sodium thiolate **2.126** and thereby afforded sulfide **2.127**. N-alkylation with 2-(4-bromobutyl)-1,3 dioxolane followed by sulfide-to-sulfone oxidation yielded **2.129**. Deprotection and intramolecular Julia-Kocienski olefination lead to **2.131**. This was the first example of a highly diastereoselective formation a Z alkene in an eight-membered ring *via* an intramolecular Julia-Kocienski reaction and the first example of such a process in complex natural product synthesis. C-acylation with dimethyl carbonate completed the synthetic sequence for the second partner **2.118** (Scheme 34).



Scheme 34: Synthesis of second partner 2.118

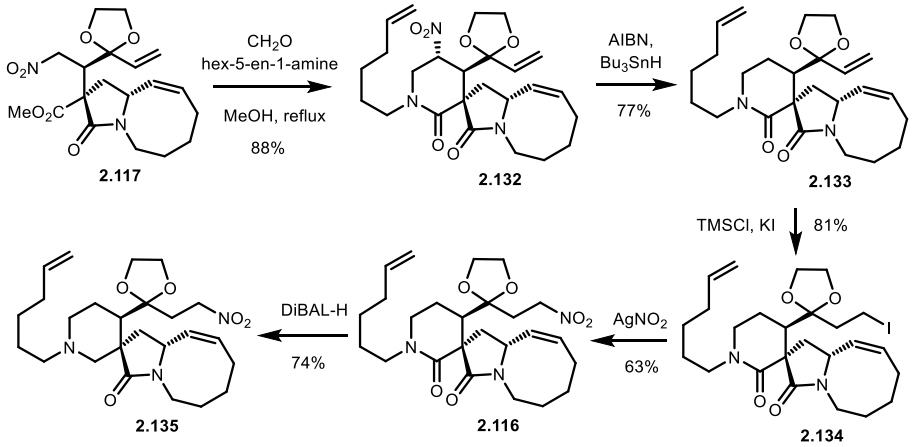
With the two partners **2.118** and **2.119** in hand, unfortunately the previously used organocatalysed Michael addition was not viable. [19] Nonetheless, desirable reactivity was observed when KMDS was used with crown-ether. Moderate diastereoselectivity was witnessed towards the target isomer (d.r. = 73:27:0:0) but the diastereomers were easily separated by flash column chromatography and the desired product **2.117** was obtained in 65 % yield (Scheme 35).



Scheme 35: Michael addiction leading to 2.117

[19] (a) Jakubec, P.; Cockfield, D. M.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 16632. (b) Rigby, C. L.; Dixon, D. *J. Chem. Commun.* **2008**, 3798. (c) Jakubec, P.; Kyle, A. F.; Calleja, J.; Dixon, D. J. *Tetrahedron Lett.* **2011**, 52, 6094.

Performing the nitro-Mannich/lactamization cascade[20], the nitro-ester **2.117** was reacted with formaldehyde and hex-5-en-1-amine to afford piperidinone **2.132**. Removal of the nitro group under modified Ono's conditions[21] gave the tricyclic core **2.133**. Conversion of alkene **2.133** to nitro **2.116** was made possible by anti-Markovnikov addition of HI and reaction with silver nitrite in 63 % yield. Reduction of the piperidinone **2.116** to piperidine **2.135** was performed with DiBAL-H in very good yield without undesired reduction of nitro group (Scheme 36).

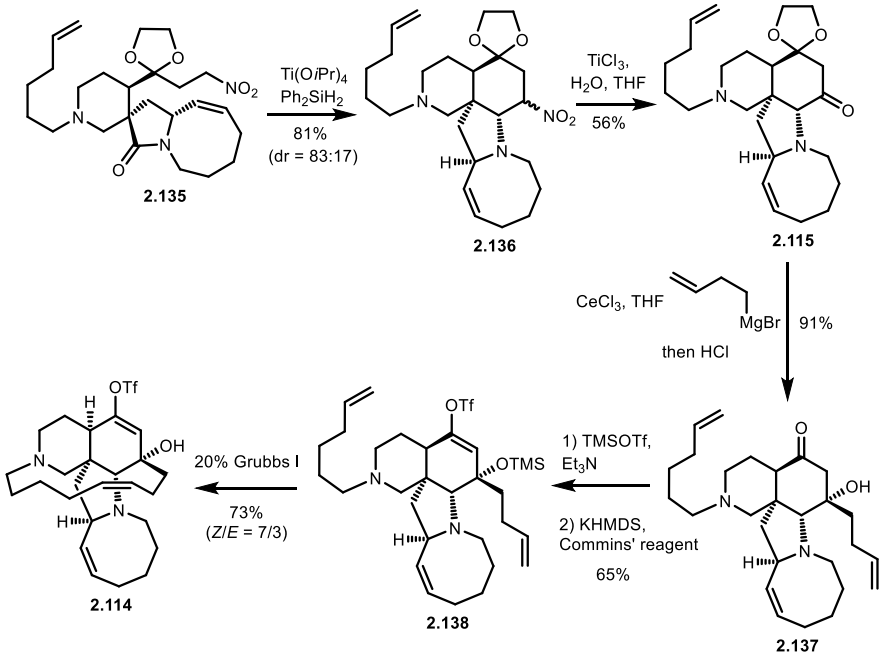


Scheme 36: Synthesis of piperidine 2.135

Pleasingly, Buchwald's conditions[22] applied to **2.135** provided the necessary chemoselectivity and reactivity profile to give **2.136** in an 83:17 ratio and 81 % yield. A McMurry modification of a reductive Nef reaction[23] employing titanium trichloride in a water-THF mixture gave the key tetracyclic ketone **2.115**. A highly face selective addition of butenyl cerium derivative giving **2.137** followed by TMS protection and enol triflate formation provided **2.138** in a decent yield of 65 %. The last step was a *Z*

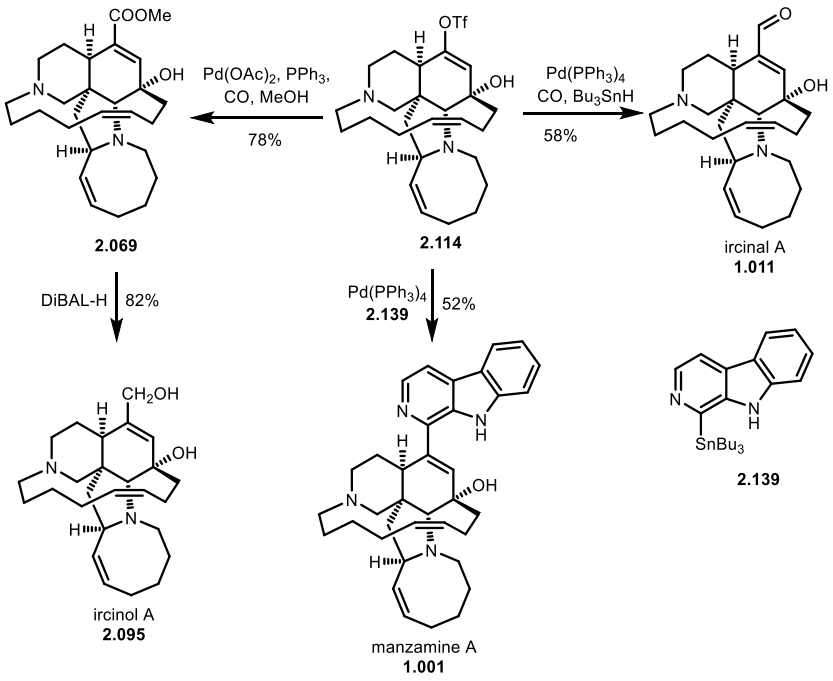
[20] Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10* (19), 4267.
[21] Ono, N.; Kaji, A. *Synthesis* **1986**, 693.
[22] Bower, S.; Kreutzer, K. A.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **1996**, *35*, 1515.
[23] Ballini, R.; Petrini, M. *Tetrahedron* **2004**, *60*, 1017.

selective RCM with Grubbs' first-generation catalyst and an acid work-up to afford the key intermediate **2.114** (Scheme 37).



Scheme 37: Synthesis of key intermediate 2.114

With access to the key late-stage intermediate **2.114** established, the cross-coupling of the β-carboline moiety was investigated. The Stille type coupling with tributylstannylated β-carboline **2.139** was successful and provided manzamine A 1**.001** in 52 % yield. Exploration of **2.114** reactivity was performed to obtain ircinal A **1.011** in 58 % yield with carbon monoxide and methyl ircinate **2.069** in 78 % yield. This ester was reduced in ircinol A **2.095**, thereby establishing proof that enol triflate **2.114** is an extremely suitable intermediate towards many members of the manzamine family (Scheme 38).



Scheme 38: Synthesis of manzamine A, ircinal A and ircinol A

5. Summary of achieved syntheses

To wrap it up, the best synthesis in overall yield has been proposed by Fukuyama *et al.* with almost half a percent yield at the outcome of 31 total steps. The shortest synthesis has derived from the work of Dixon *et al.* with a total of 23 steps and a longest sequence of not more than 18 steps (Table 1).

Synthesis	Longest linear sequence	Total steps	Overall yield %
MZA Winkler 1998	34	37	0.043
MZA Martin 2002	21	24	0.088
MZA Fukuyama 2010	27	31	0.493
MZA Dixon 2012	18	23	0.054

Table 1: Summary of syntheses

From a more personal point of view, the synthesis proposed by Fukuyama is really long compared to the others. Martin was unfortunate as Winkler published just few months before he could finish his final steps (Even if officially, the full paper was published in 2002, the communication about almost the total synthesis went out in 1999). However, the polycyclization using Grubbs' catalyst was overambitious and let to many practical complications. On my opinion, Dixon developed the best synthesis, through several methodologies and with a possibility to extend the scope as final step. Unfortunately, the use of metals such as tin as last step makes this approach unsuitable for pharmacological applications.

Chapter III

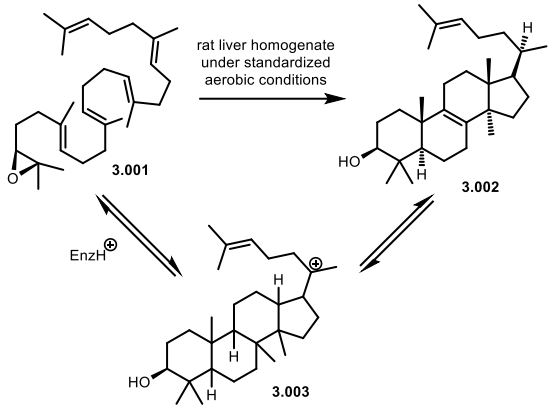
Polycyclization, Previous Work and Objectives

In this chapter I will present a short introduction on polycyclization, directly followed by early work and methodologies of anionic polycyclization developed in the Markó group. Most of these principles will be useful to understand the objectives of this thesis.

1. Polycyclization

Cascade cyclization or polycyclization reactions are extremely useful in organic chemistry. This is mostly due to the fact that this process can fix several chiral centres and cycles in one step. Synthetic chemists found various ways to apply new polycyclization protocols to reach complex targets.[1] One of the most famous polycyclizations was demonstrated by Corey *et al.*[2] and consists in the polycyclization of epoxy-squalene **3.001** into sterol **3.002** using rat liver homogenate (Scheme 1).

[1] Anderson, E. A. A. *Org. Biomol. Chem.* **2011**, *9*, 3997.
[2] Corey, E. J.; Russey, W. E.; Ortiz, P. R. *J. Am. Chem. Soc.* **1966**, *88*, 4750.

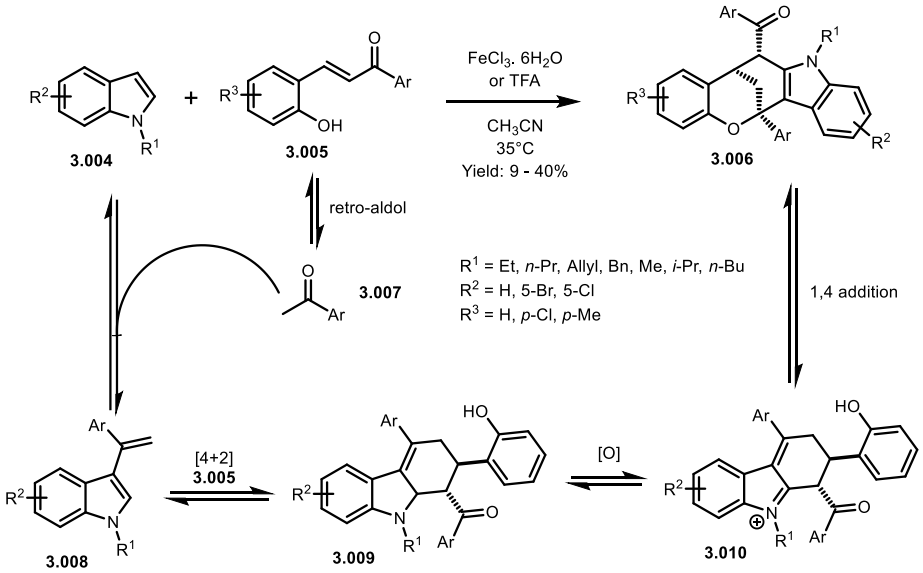


Scheme 1: Squalene epoxide 3.001 polycyclization

Four different types of cyclization can be found, i.e. cationic such as for **3.001**, anionic, metal catalysed and finally, radical process. Since in this thesis we solely focus on the use of indole to reach our target, the following selected examples of polycyclizations will be based on indole chemistry and will set an example for the four types of conditions.

a. Cationic Polycyclization

In 2018, *Bu et al.*[3] proposed a Lewis acid promoted cationic polycyclization to synthetize the complex indole moiety **3.006** using substituted indoles of type **3.004** and two equivalents of styryl ketone **3.005**. The authors created two new cycles and 4 chiral centres. They proposed a mechanism based on retro-aldol from **3.005** to **3.007**, followed by a condensation with indole moiety **3.004**. Then, a [4+2] cyclization could take place between **3.008** and **3.005**. Finally, the cyclized product **3.009** could be oxidized by air/oxygen and undergo a Michael addition to produce **3.006** (Scheme 2).

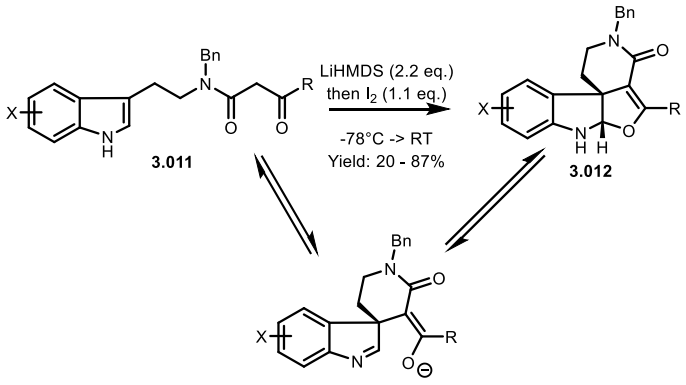


Scheme 2: Example of cationic polycyclization

[3] (a) Wang, W.; Bai, X.; Jin, S.; Guo, J.; Zhao, Y.; Miao, H.; Zhu, Y.; Wang, Q.; Bu, Z. *Org. Lett.* **2018**, *20*, 3451. (b) Guo, J.; Bai, X.; Wang, Q.; Bu, Z. *J. Org. Chem.* **2018**, *83*, 3679.

b. Anionic Polycyclization

In 2012, Ma *et al.*[4] built a complex indoline scaffold **3.012** by anionic polycyclization with lithium hexamethyldisilazide and iodide. From indole **3.011**, this process required two equivalents of LiHMDS and one equivalent of I_2, however, it allows the concomitant formation of two chiral centres and two cycles in one step. The authors proposed a mechanism based on oxidative coupling at first to obtain indoline **3.013** then cyclizing into the target molecule **3.012**.

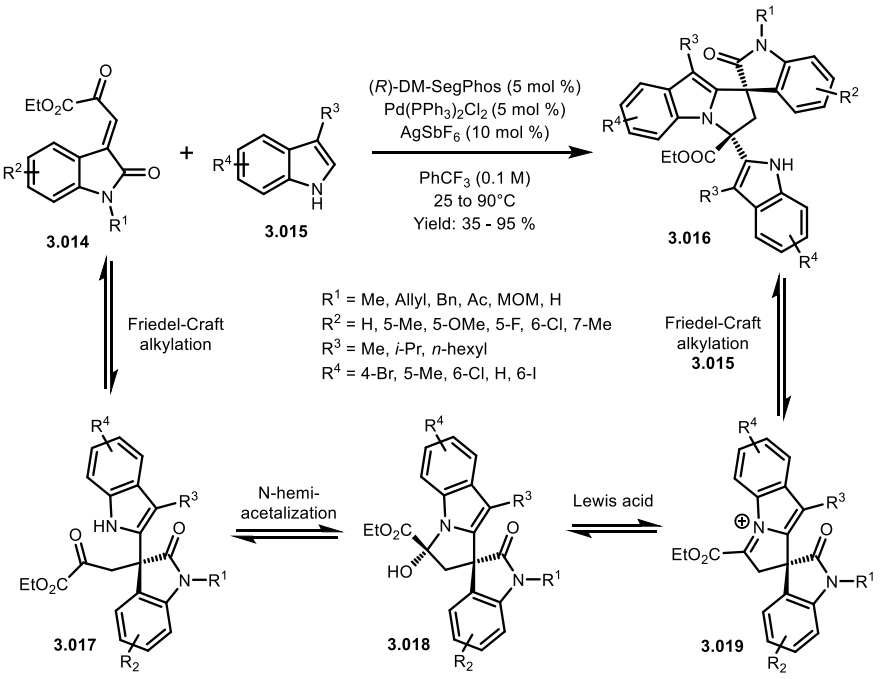


Scheme 3: Example of anionic polycyclization

[4] Fan, F.; Xie, W.; Ma, D. Org. Lett. *2012*, **14**, 1405.

c. Metal catalysed Polycyclization

An example of polycyclization by Wang *et al.*[5] is based on an asymmetric palladium silver catalyst to obtain tri-indole compound **3.016**. The authors proposed a mechanism based on a Friedel-Crafts alkylation of indole **3.015** on oxindole **3.014** to get the intermediate **3.017**. Following ring-closure under Lewis acidic conditions, iminium **3.019** was obtained. Finally, a second Friedel-Crafts alkylation was proposed to create the target molecule **3.016** (Scheme 4).

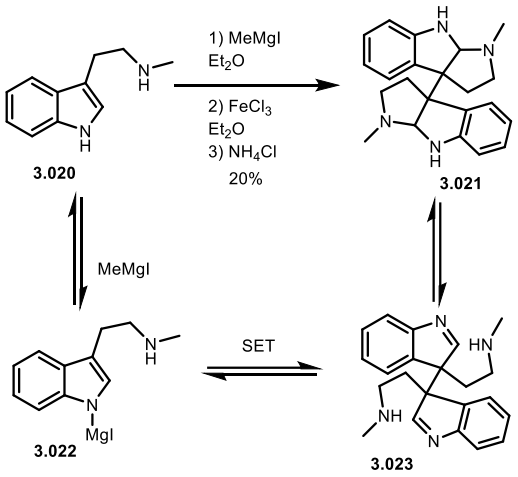


Scheme 4: Palladium/Silver catalysed polycyclization

[5] Li, N-K.; Zhang, J-Q.; Sun, B-B.; Li, H-Y.; Wang, X-W. *Org. Lett.* **2017**, *19*, 1954.

d. Radical Polycyclization

The final example of polycyclization was published in 1964 by Scott *et al.*[6] and is based the total synthesis of Chimonanthine **3.021** as one-step biosynthetic model. A solution of commercially available methyl tryptamine **3.020** was added on methyl Grignard to form the indole-magnesium **3.022** reacting with iron trichloride to produce bis-indoline **3.023**. Finally, double intramolecular cyclization of amine on indoline provided the desired compound **3.021** (Scheme 5).

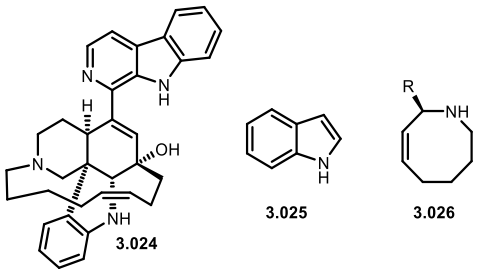


Scheme 5: Radical polycyclization

[6] (a) Scott, A. I.; McCapra, F.; Hall, E. S. *J. Am. Chem. Soc.* **1964**, *86*, 302. (b) Hall, E. S.; McCapra, F.; Scott, A. I. *Tetrahedron* **1967**, *23*, 4131.

2. Previous work

The idea of indole-manzamine **3.024** started in the early 1990's in Sheffield in the hands of Mike Southern (Ph.D. thesis in 1994).[7] Indole **3.025** is a cheap and biocompatible scaffold as it can be found in alkaloids, pigments and proteins. This building block allows us to directly start the key steps for the central core assembly without performing the azocine **3.026** synthesis (*Cf.* chapter II) (Scheme 6).

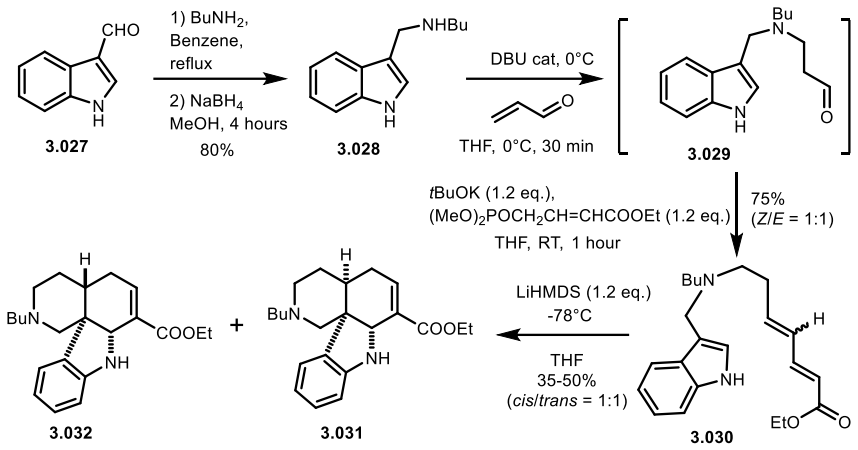


Scheme 6: Indole-manzamine 3.024, indole 3.025 and azocine 3.026

[7] Southern, M. *PhD Thesis* **1994**, University of Sheffield

3. First Generation of Anionic Polycyclization

Mike Southern proposed an intramolecular cyclization of the polyunsaturated ester **3.030** in a five-step process to forge the indole-manzamine central core **3.031**. These operations were coined “Anionic Polycyclization”. Unfortunately, this procedure suffered from weaknesses in that there was no control of the double bond geometry of the polyunsaturated system in **3.030** and that low yield of the polycyclization itself was poor. However, this method exhibited an interesting potential of simplicity and decent yield of 30 % over 5 steps. (Scheme 7).[8]



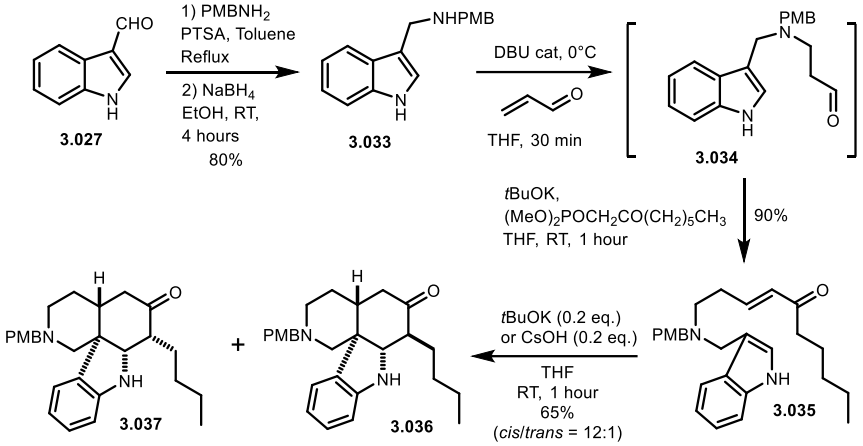
Scheme 7: First generation of anionic polycyclization

X-ray diffraction was performed on *trans*-**3.032** to confirm the hypothesized diastereoselectivity. The structure of *cis*-**3.031** was deduced from correlations of its spectroscopic properties with those of **3.032**.

[8] Markó, I. E.; Southern M. J.; Adams H. *Tetrahedron Lett.* **1992**, *33*, 4657.

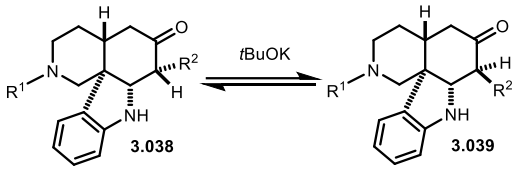
4. Second Generation of Anionic Polycyclization

Laurent Turet used enone **3.035** as cyclization precursor. He found that *t*BuOK or CsOH could promote the reaction. Double cyclization proceeded with a nice yield of 65 % and lead to *trans*-**3.036** and *cis*-**3.037** with an unfortunate preference for **3.037** (Scheme 8).[9]



Scheme 8: Second generation of anionic polycyclization

The *trans*-**3.038** could come from epimerization of the α-keto hydrogen of *cis*-**3.039** by the action of *t*BuOK (Scheme 9).

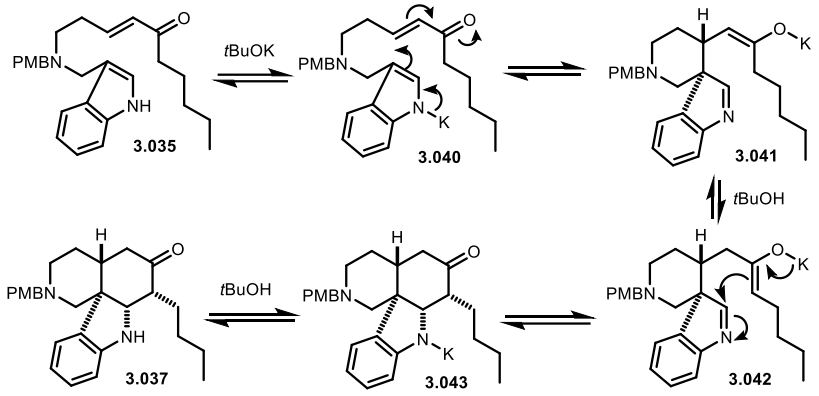


Scheme 9: Epimerisation 3.038-3039

A simple mechanism was proposed and implied metalation of the indole nitrogen of **3.035** by *t*BuOK, followed by Michael addition of the indole 3 position on the enone in **3.040**. Potassium enolate **3.041** was then postulated to equilibrate under the action of *t*BuOH to bring forth enolate

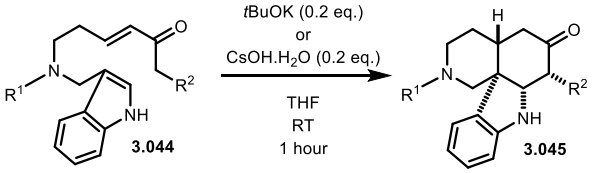
[9] (a) Turet, L.; Markó, I. E.; Tinant, B.; Declercq, J-P.; Touillaux, R. *Tetrahedron Lett.* **2002**, *43*, 6591. (b) Turet, L. *PhD Thesis* **2004**, Université catholique de Louvain.

3.042 that cyclized to potassium amide **3.043**. Finally, reprotonation with *t*BuOH provided the tetracycle **3.037** (Scheme 10).



Scheme 10: Mechanism of polycyclization

The methodology was extended to various side chains. Entries **3**, **5** and **7** were designed for macrocyclization but unfortunately could not promote the formation of **3.045**. The yields in entries **9** & **10** are slightly lower with the substrate bearing an N-allyl (Scheme 11 and Table 1).



Scheme 11: Application of polycyclization

Entry	R1	R2	Yield (%)
1	PMB	Et	45
2	PMB	Bu	60
3	PMB	$(CH_2)_2CC(CH_2)_4Cl$	49
4	PMB	H	55
5	Boc	$(CH_2)_2CC(CH_2)_4Cl$	64
6	$(CH_2)_4CCCH_3$	$(CH_2)_2CCCH_3$	49

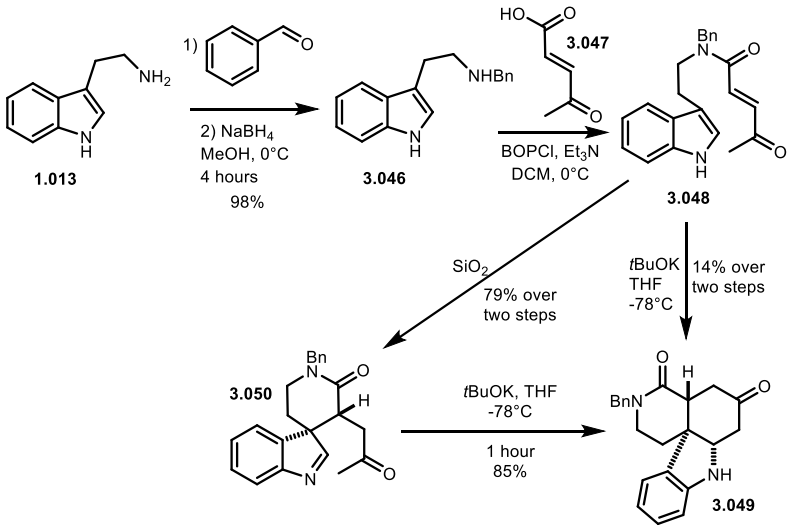
7	$(CH_2)_4CCCH_2OTBS$	H	38
8	$(CH_2)_4CHCH_2$	$(CH_2)_2CHCH_2$	61
9	Allyl	Et	35
10	Allyl	Bu	38

Table 1: Application of polycyclization

5. ACNO derivatives through Acid/Base-Polycyclization

On his way towards the synthesis of *Aspidosperma* and *Strychnos* alkaloids, Nicolas Heureux used an Acid/Base-catalyzed polycyclization.[10]

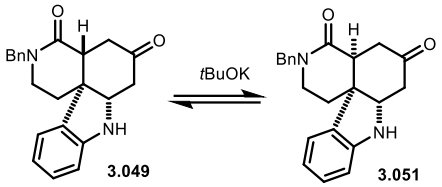
Reduction of the imine derived from tryptamine **1.013** and benzaldehyde gave the secondary amine **3.046** which underwent amide coupling with **3.047** providing the polycyclization precursor **3.048**. Direct polycyclization with *t*BuOK afforded the product **3.049** in poor yield (14 %). This could be tremendously improved by a two-step process up to 67 %, producing the monocyclic intermediate **3.050** in the presence of silica gel. This indolenine-ketone **3.050** could perform a ring closure with *t*BuOK leading to **3.049** (Scheme 12).



Scheme 12: Acid-base polycyclization

[10] (a) Heureux, N.; Wouters, J.; Markó, I. E. *Org. Lett.* **2005**, *7*, 5245. (b) Heureux, N.; Wouters, J.; Norberg, B.; Markó, I. E. *Org. Biomol. Chem.* **2004**, *4*, 3898. (c) Heureux N. *PhD Thesis* **2006**, Université catholique de Louvain.

At the same time, Nicolas detected **3.051** as a major side product of the reaction from **3.050** to **3.049** considering the temperature as the primary factor for its production because of the basicity of *t*BuOK. At -78°C, only **3.049** was recovered (Scheme 13).



Scheme 13: Epimerisation 3.049-3.051

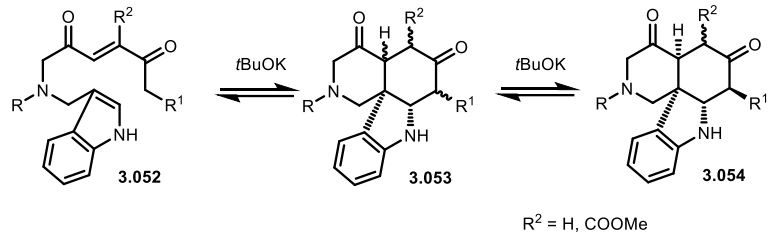
6. Objectives of this Ph.D. Thesis

The main objective is to find the shortest possible way to the tetracyclic core of indole-manzamine **3.024** using a new methodology of Anionic Polycyclization.

This new Anionic Polycyclization would be the outcome of everything understood in the previous ones:

a) *t*BuOK proved to be a good base for this kind of reaction
b) α-keto-hydrogen can be epimerized in **3.038-3.039**
c) α-amido-hydrogen can be epimerized in **3.049-3.051**
d) polycyclization can be successful on ene-dione system

Combined, these points led to the following idea: using *t*BuOK as base for an ene-dione indole **3.052** polycyclization and if needed *t*BuOK should be able to epimerise **3.053** into **3.054**. This could be tested with a simple ene-dione R^2 = H or with a Knoevenagel condensate R^2 = CO_2Me (Scheme 14).



Scheme 14: Thesis Project

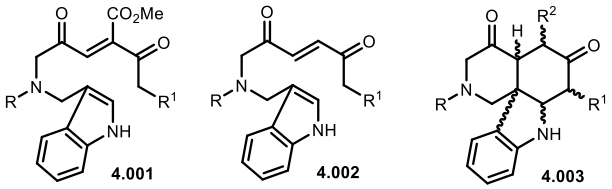
The second objectives are:

- Using cheap starting materials such as indole **3.025**
- Look for bioactivities of our newly made products
- Obtain the correct diastereoisomer **3.054**
- Finish the synthesis of indole-manzamine **3.024**

Chapter IV

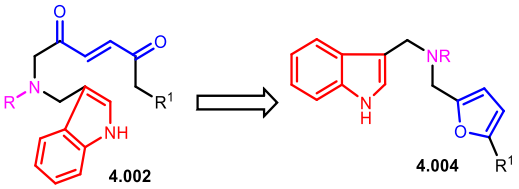
Attempts to reach ene-dione moiety

As has been extensively discussed in the previous chapter, we aimed at synthetizing the Knoevenagel adduct **4.001** or ene-dione **4.002** to set the stage for the cyclization into the tetracycle **4.003** (Scheme 1).



Scheme 1: Target molecule and precursors

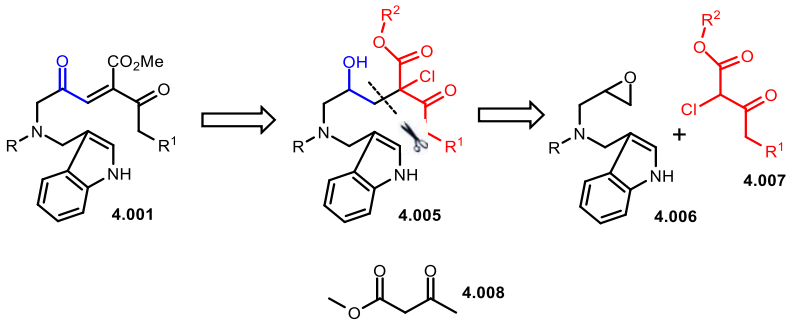
According to literature, the easiest access to ene-dione **4.002** would be the oxidation of furan **4.004** (in blue). Unfortunately, the presence of both, the indole (in red) and the amine (in pink) in **4.004** might be problematic towards oxidation. Moreover, the use of protections would go against our objective of a short synthesis. However, this chemistry could serve as a back-up plan in case other pathways failed (Scheme 2).



Scheme 2: Ideal retrosynthesis

1. First disconnection with epoxide and β-keto-ester

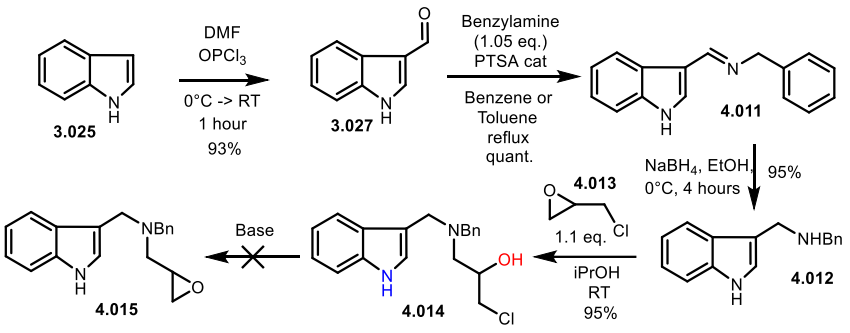
The highly activated Michael-acceptor **4.001** was assigned as a first target and should be accessible from the oxidation of alcohol **4.005** followed by the elimination of HCl to forge the unsaturation **of 4.001**. Epoxide opening of **4.006** with chloro-β-keto-ester **4.007** should provide the requested alcohol **4.005**. The presumably poor nucleophile **4.007** will be, at first, replaced by its non-chlorinated and sterically more appealing homologue **4.008** to obviate this issue (Scheme 3).



Scheme 3: Disconnection epoxide and β-keto-ester

The synthesis of epoxide **4.014** started with high yielding formylation of indole **3.025** to **3.027**.[1] This operation was followed by reductive amination with benzylamine, allowing access to **4.012**. Epichlorohydrin **4.013** was selected as 1,3-bis-electrophile and the addition of amine **4.012** successfully led to **4.014**. Unfortunately, the cyclization to epoxide **4.015** failed. The reason is the proximity of the pK_a range of a secondary alcohol OH (in red) and NH of indole (in blue). This deprotonation only afforded an undesirable mixture of products. We suspected the formation of cyclized product by 5-*exo-tet* or 6-*endo-tet* cyclization and even intermolecular reaction. Unfortunately, these potential products cannot be useful for us (Scheme 4).

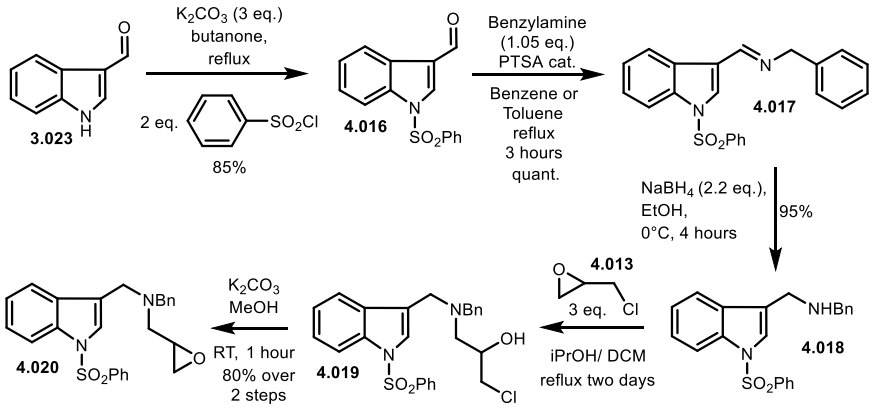
[1] Smith, G. F. *J. Chem. Soc.* **1954**, 3842.



Bases tested: A = K_2CO_3 in MeOH, B = NaOH in MeOH, C = *t*BuOK in THF,
D = *t*BuOK in *t*BuOH, E = K_2CO_3 in H_2O/THF, F = NaOH in H_2O/THF, G = Et_3N in DCM.

Scheme 4: Synthesis of 4.015

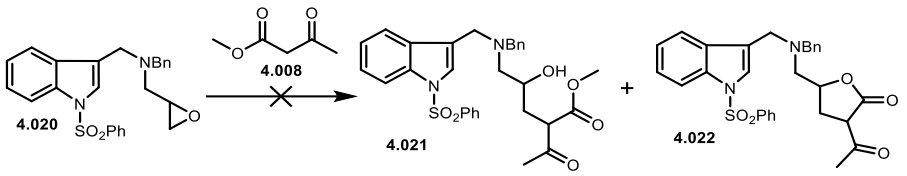
The easiest way to confirm this issue would be the removal of the acidic proton attached to the indole. Sulfonamide is a classic choice for indoles and **3.027** was reacted with benzenesulfonyl chloride to afford the sulfonamide **4.016**.[2] This compound underwent reductive amination with benzylamine yielding **4.018**. Unfortunately, the presence of this protection drastically increased the steric hindrance around the secondary amine, and the same reaction as before required stronger conditions to convert epichlorohydrin **4.013** into **4.019**. The cyclization into epoxide **4.020** was performed with a good yield of 80 % from amine **4.018** (Scheme 5).



Scheme 5: Synthesis of epoxide 4.020

[2] Tholander, J.; Bergman, J. *Tetrahedron* **1998**, *55*, 6243.

As explained before, the epoxide opening tests were performed with the dehalogenated β-keto-ester **4.008**. Various conditions were tested for this reaction. There are two major potential products, namely gamma-hydroxy-ester **4.021** or the lactone **4.022**. Both of them could come from the reaction between **4.020** and the anion of **4.008**. To our greatest dismay, none of them was observed and only starting material was recovered. One hypothesis is that the extreme steric hindrance brought forth by the phenylsulfonamide moiety and benzyl on the amine shield the epoxide from incoming nucleophiles (Scheme 6).



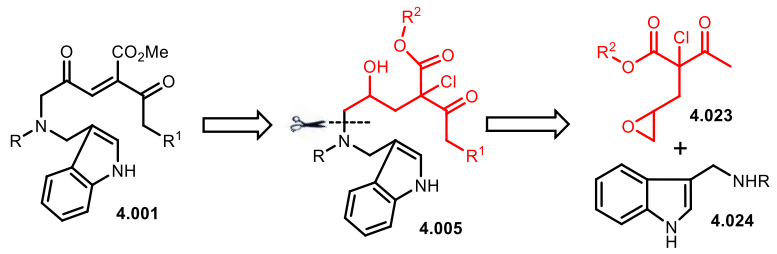
Scheme 6: Epoxide opening with β-keto-ester

Due to this issue and the use of protecting group, we reinvestigated our disconnection.

2. Second disconnection with epoxide and amine

a. Synthesis of chlorine epoxide

The target molecule is again **4.001** and was planned to come from the oxidation of alcohol **4.005** and elimination of HCl. Contrary to the initial strategy, the epoxide **4.023** would be opened by the more nucleophilic amine **4.024**. The opening of epichlorohydrin under these conditions proved to be successful in the past (Scheme 7).

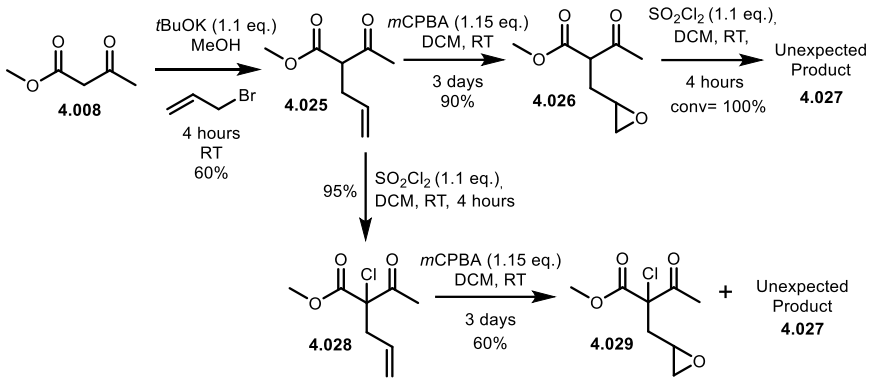


Scheme 7: Second disconnection

The synthetic sequence that should allow access to **4.023** started with C-allylation of keto-ester **4.008** with allyl bromide to lead to mono-allyl **4.025** in 60 % yield (the 40 % remaining are starting material and undesired bis-allylated product).[3] At this point we were facing two possibilities, chlorination or a Prilezhaev epoxidation. So, we tried both to see which one is more convenient. Epoxidation of **4.025** with *m*CPBA leads to the desired epoxide **4.026**. Chlorination with SO_2Cl_2 was performed to afford the unexpected product **4.027**. This new product was a single compound by NMR and since the same mass as **4.023** was found by mass spectroscopy, **4.027** is thought to be a structural isomer and a rearranged product of our target. Two hypotheses can be formulated from those results. First, the product is unstable and rearranges. Second, the conditions promote the rearrangement. The second hypothesis is extremely easy to verify, mono-allylated product **4.025** was chlorinated with SO_2Cl_2 into chloro-β-keto-ester

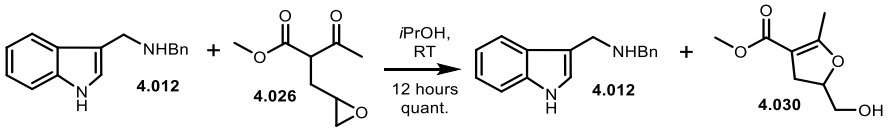
[3] Kaoru, N.; Miyai, T.; Ashish, N.; Shinzaburo, O.; Atsuyoshi, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1179.

4.028. Epoxidation of **4.028** afforded the same unexpected product **4.027** together with target molecule **4.029** (Scheme 8).



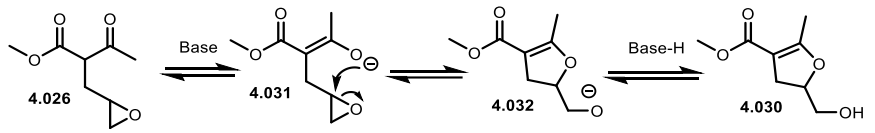
Scheme 8: Oxidations of allyl-β-keto-ester 4.025

The coupling between amine **4.012** and epoxide **4.026** was tested and furnished two products: starting material **4.012** and a new product **4.030**. Again, NMR revealed the presence of a single product, not a mixture of diastereoisomers and mass spectrometry confirmed that **4.026** and **4.030** were isomers. (Scheme 9).



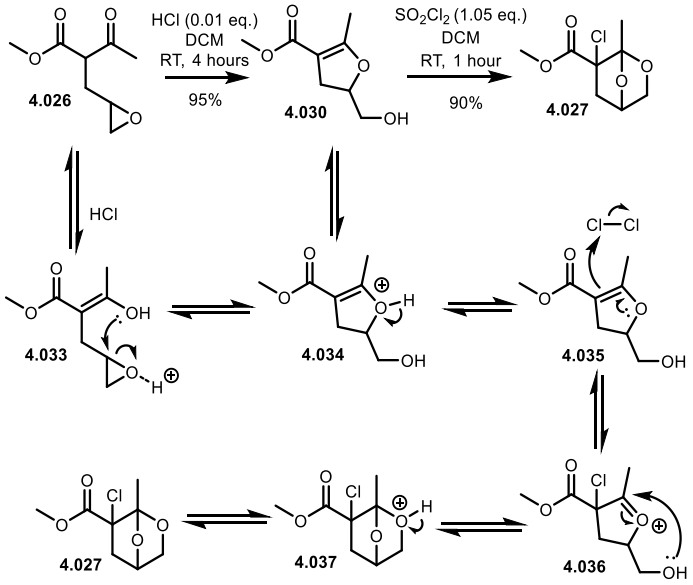
Scheme 9: Coupling between amine and epoxide

The presence of **4.030** can be explained by first deprotonation of **4.026** by the amine, leading to **4.031**. This stabilized enolate could perform a 5-*exo*-*tet* cyclization into dihydrofuran **4.032** which upon reprotonation forms **4.030**. Being a catalytic process, one equivalent of amine **4.012** was far more than enough to quickly convert of the epoxide **4.026** into **4.030** (Scheme 10).



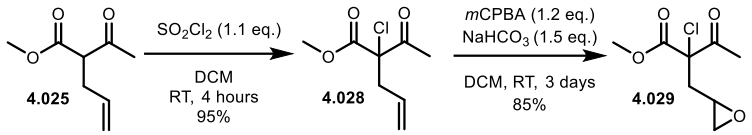
Scheme 10: Proposed mechanism towards 4.030

The 5-*exo*-*tet* cyclization was promoted under basic conditions towards **4.030**, so similar conditions were tested with acid. Epoxide **4.026** was submitted to the presence of dry hydrochloric acid and as expected, afforded **4.030**. There is a suggestion that this transformation occurs *via* conjugated enol **4.033** and intramolecular 5-*exo*-*tet* cyclization on activated epoxide to afford **4.034.** Loss of hydrogen formed **4.030**. In case of traces of acid in SO_2Cl_2 during the reaction with **4.026** we can assume that the formation of **4.030** is the first step towards **4.027**. The chlorination of **4.030** was tested with SO_2Cl_2 and as planned we obtained **4.027** but this time, we have enough data to understand what has happened. Cyclic enol **4.035** performs an attack on chlorine (or sulfuryl chloride) providing the α-chloro-oxonium **4.036** further undergoing an intramolecular 5-*exo*-*trig* cyclization. By loss of a proton, the resulting product **4.037** delivers the unexpected material **4.027** (Scheme 11).



Scheme 11: Cyclization processes during chlorination of epoxide 4.026

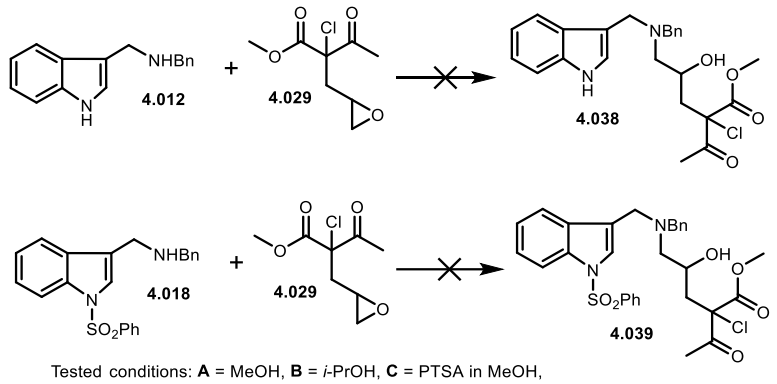
To circumvent this problem, the final procedure consisted in chlorination of **4.025** into **4.028** followed by epoxidation with *m*CPBA in the presence of sodium hydrogencarbonate (Scheme 12).



Scheme 12: Synthesis of chloro-epoxide 4.029

b. Coupling tests

The coupling was tested with both, unprotected amine **4.012** or protected amine **4.018** in the presence of chloro-epoxide **4.029** to hopefully deliver our target **4.038.** No matter the conditions tested, amine **4.012** inevitably leads to decomposition of chloro-epoxide **4.029** or of starting material. As expected, amine **4.018** did not react at all (Scheme 13).



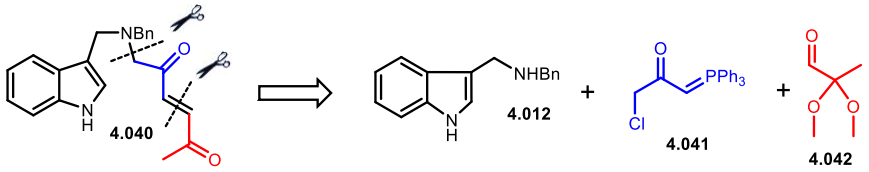
Tested conditions: **A** = MeOH, **B** = *i*-PrOH, **C** = PTSA in MeOH,
D = PTSA in DCM, **E** = CSA in DCM, **F** = TFA in DCM,
G = TFA in MeOH, **H** = CSA in MeOH.

Scheme 13: Coupling between amines and epoxides

Facing all these setbacks, we decided to change the target to the simple ene-dione **4.002** without the ester moiety. This ene-dione **4.002** should be less active for the first cyclization (Knoevenagel adduct in the first case against enone in this case) but we expected less problems to obtain it.

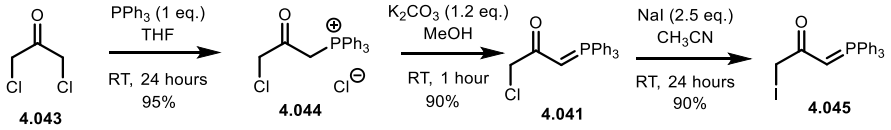
3. Wittig approach

A new disconnection was considered, based on a Wittig reaction between **4.041** and **4.042** and an S_N2 between **4.012** and **4.041** (Scheme 14).



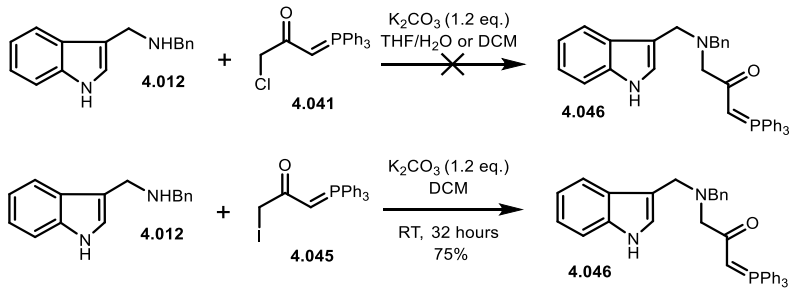
Scheme 14: Disconnection based on Wittig reaction

Phosphorane **4.041** was synthesised in two steps with excellent yield from 1,3 dichloroacetone **4.043**.[4] Those steps were followed by a Finkelstein halogen exchange to afford **4.045** in good yield (Scheme 15).



Scheme 15: Chloro and iodo-phosphorane synthesis

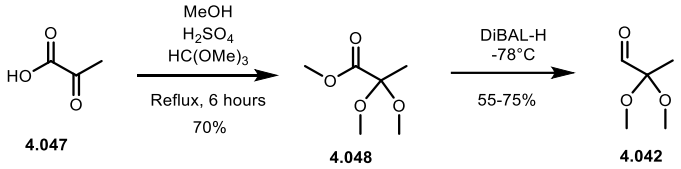
Both ketohalides **4.041** and **4.045** were tested under the S_N2 reaction conditions with amine **4.012**. No reaction was observed with **4.041**, on the other hand, the iodinated material **4.045** lead to **4.046** in a good yield of 75 % (Scheme 16).



Scheme 16: S_N2 between amine 4.012 and Phosphorane

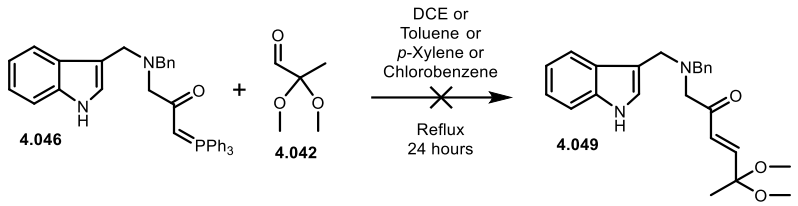
[4] Taillier, C.; Hameury, T.; Bellosta, V.; Cossy, J. *Tetrahedron* **2007**, *63*, 4472.

Pyruvic acid **4.047** was protected and esterified with methanol to produce the ester **4.048**.[5] Ensuing reduction with DiBAL-H afforded aldehyde **4.042** in good yield (Scheme 17).



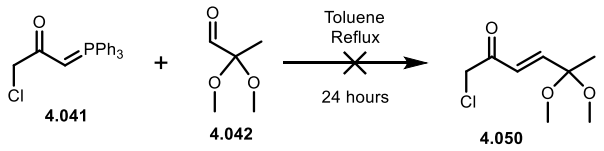
Scheme 17: Synthesis of 4.042 from pyruvic acid 4.047

The Wittig reaction was tested with keto-phosphorane **4.046**. A plethora of high boiling point solvents were used to perform this reaction, inclusive of dichloroethane, toluene, *p*-xylene and chlorobenzene. Unfortunately, none of these conditions leads to the desired enone **4.049**, presumably due to the low nucleophilicity of keto-phosphorane **4.046** and the high α steric hindrance of aldehyde **4.042** (Scheme 18).



Scheme 18: Wittig reaction towards 4.049

To support his hypothesis, reaction between chlorinated compound **4.041** and aldehyde **4.042** was tested but to no avail (Scheme 19).

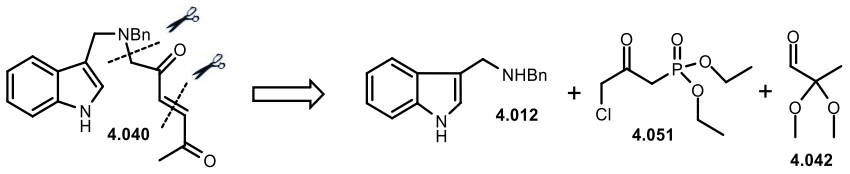


Scheme 19: Proof of low reactivity of 4.041

[5] Bowman, E. R. *J. Chem. Soc. Perkin Trans. I* **1982**, 1897.

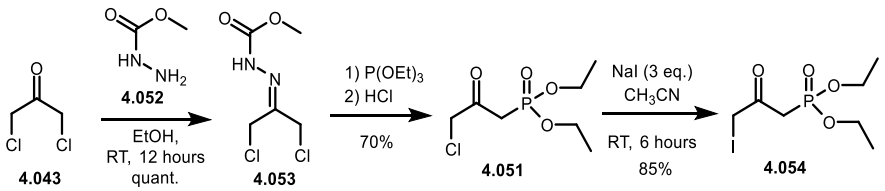
4. Horner-Emmons approach

To improve the nucleophilicity, the β-keto-phosphorane was exchanged for a β-keto-phosphonate to set the stage for a Horner-Emmons reaction instead of a Wittig. The S_N2 between **4.012** and **4.051** was untouched (Scheme 20).



Scheme 20: Disconnection based on Horner-Emmons reaction

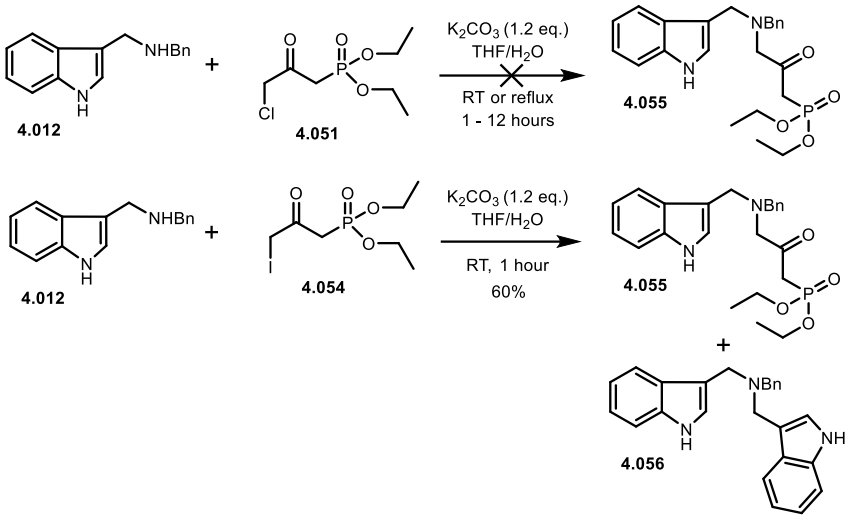
Starting from dichloroacetone **4.043**, reaction with methyl hydrazinocarboxylate **4.052** lead to **4.053**.[6] This compound underwent an Arbuzov reaction followed by hydrolysis into chloro-keto-phosphonate **4.051** and by a Finkelstein reaction to afford iodo-keto-phosphonate **4.054** (Scheme 21).



Scheme 21: Synthesis of chloro and iodophosphonate

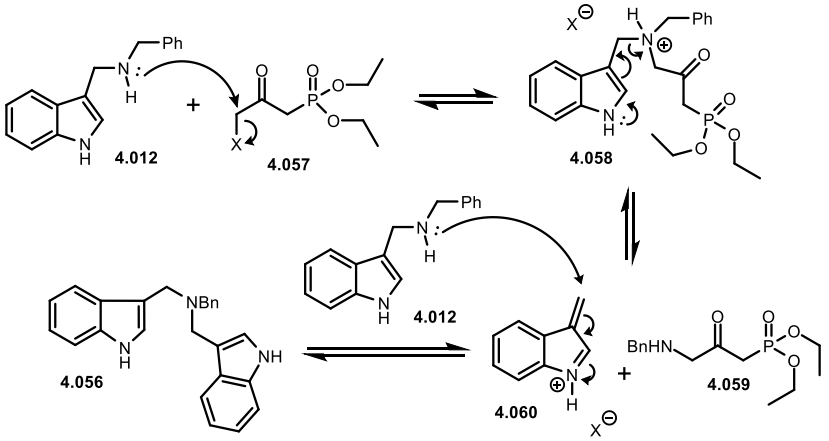
The coupling was tested between amine **4.012** and chloro-compound **4.051** or iodo compound **4.054**. Once again, the reaction with the chloro adduct was unsuccessful. The amino-keto-phosphonate **4.055** was obtained in a decent yield of 60 % with an important proportion of another product **4.056**. The NMR data of this new compound were extremely similar to amine **4.012** except that benzylic CH_2 integration was half of the required number. Therefore, we deduced an indole dimer from our analyses (Scheme 22).

[6] Corbel, B.; Medinger, L.; Haelters, J-P.; Sturtz, G. *Synthesis* **1985**, *11*, 1048.



Scheme 22: SN2 between amine 4.012 and Phosphonates 4.051 and 4.054

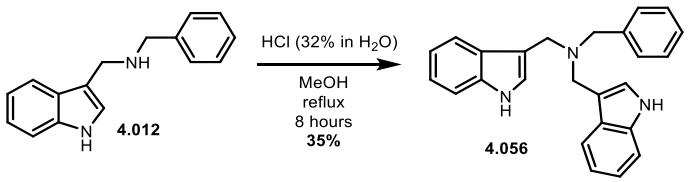
Bis-indole **4.056** could come from elimination during the S_N2 process. The attack of amine **4.012** on iodide **4.057** (X = I) provides ammonium **4.058**. Two possibilities are available for this ammonium **4.058**, first, deprotonation towards the target molecule **4.055** or elimination into ene-indoleninium **4.060** and amine **4.059**. As an extremely good electrophile **4.060** can react with starting material **4.012** to furnish bis-indole **4.056** (Scheme 23).



Scheme 23: Proposed mechanism for di-indole creation

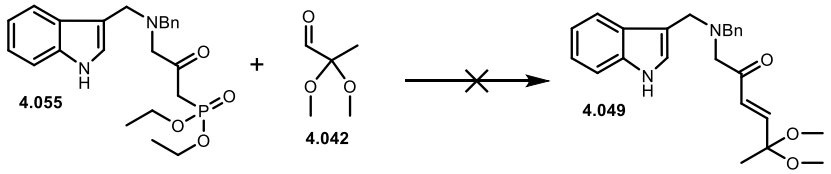
Product **4.056** was detected in most of our S_N2 reactions with amine **4.012**. It could be the major problem in our reactions with those amines. Bis-indole **4.056** was also detected in the NMR spectra of a former Ph.D. student as minor side product.

To add evidence to the degradation of the ammonium **4.058**, we performed the reaction using only HCl in aqueous methanol. After few hours of reflux, we could isolate 35 % of the bis-indole **4.056**. these data support our speculation about the degradation (Scheme 24).



Scheme 24: Formation of bis-indole 4.056 in acidic media

Reaction between keto-phosphonate **4.055** and aldehyde **4.042** was tested with various bases and solvents. None of them was successful, probably because of the NH of indole which is in the same range of pK_a as our β-keto-phosphonate function and only degradation was recovered (Scheme 25).

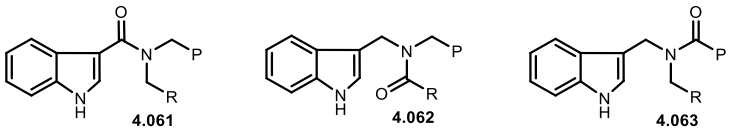


Tested conditions: **A** = *t*BuOK, THF, RT, **B** = *t*BuOK, THF, 0°C, **C** = *t*BuOK, Toluene, RT
D = *t*BuOK, Toluene, 0°C, **E** = NaHMDS, THF, -78°C, **F** = NaHMDS, Toluene, -78°C,
G = KHMDS, THF, -78°C, **H** = KHMDS, Toluene, -78°C.

Scheme 25: Horner-Emmons reaction towards 4.049

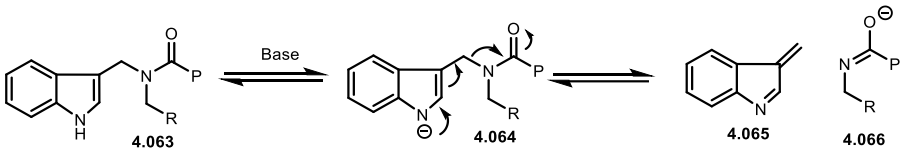
5. Horner-Emmons approach with amide

To solve both issues, production of bis-indole and indole-NH acidity, the decision of modifying the pathways was taken, again. We already protected NH of indole as sulfonamide such as **4.018**. Unfortunately, this protecting group requires drastic conditions for removal. A carbamate might offer an attractive alternative to this. To avoid the bis-indole formation, an amide modification was considered to the nitrogen, but there are three possibilities **4.061**, **4.062**, **4.063** (Scheme 26).



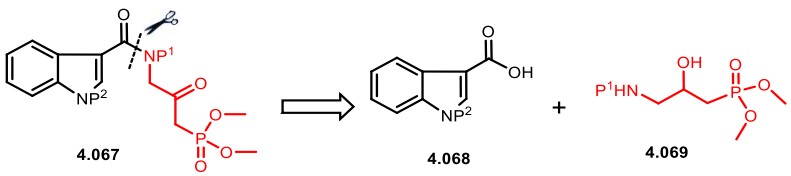
Scheme 26: possible amides

Amides in **4.062** and **4.063** were not chosen due to potential problems in the presence of base. We postulate the same elimination in basic medium as is observed in acidic conditions. Deprotonation of **4.063** (for example) could lead to **4.064** which can fragment into ene-indolenine **4.065** and **4.066** (Scheme 27).



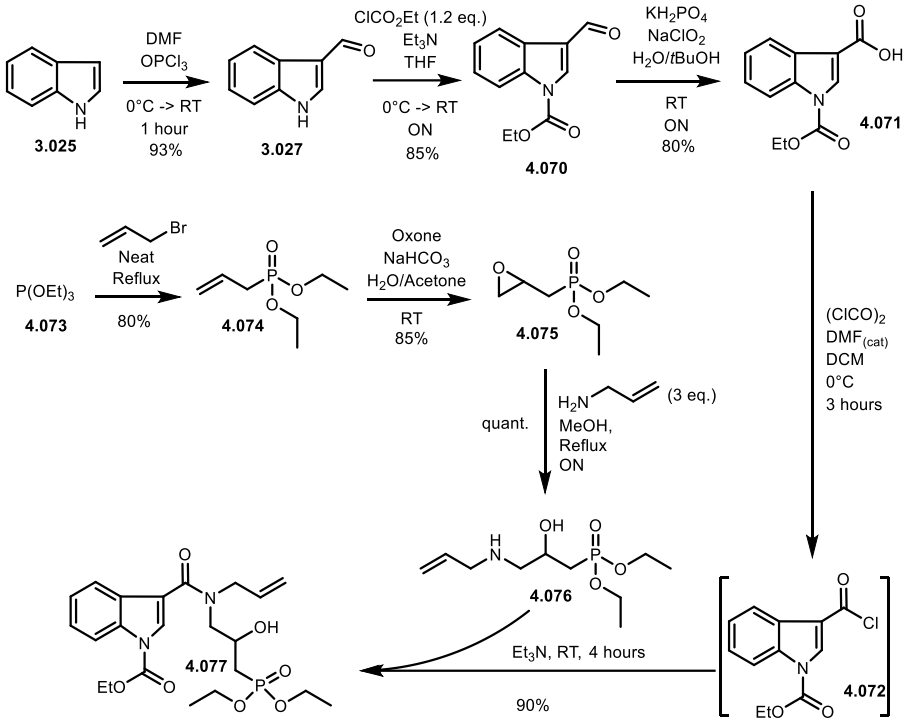
Scheme 27: Elimination in basic media

The new disconnection envisioned here is based on amide coupling between **4.068** an oxidized form of Vilsmeier adduct **3.027**, and the aminol **4.069** (Scheme 28).



Scheme 28: Amide disconnection

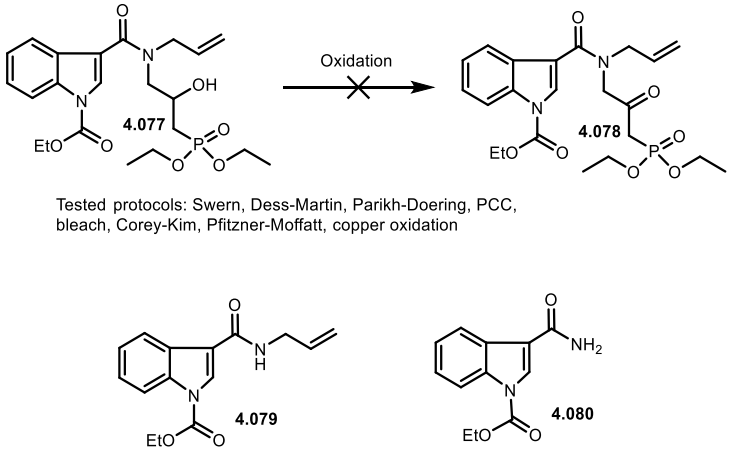
The synthesis starts with a Vilsmeier-Haack reaction followed by protection of indole as carbamate **4.070** and finally, Pinnick oxidation into acid **4.071**. At the same time, Arbuzov-Michaelis reaction was conducted on triethylphosphite **4.073** with allyl-bromide resulting in allylphosphonate **4.074**[7] which was epoxidized with oxone and acetone mixture into **4.075**. The epoxide **4.075** reacted with allylamine to afford phosphonoaminol **4.076** in an excellent overall yield. Acid **4.071** was activated by oxalyl chloride into **4.072** and reacted with aminol **4.076** to furnish **4.077** in 90 % yield (Scheme 29).



Scheme 29: Synthesis of alcohol 4.077

[7] Platonov, A. Yu.; Sivakov, A. A.; Chistokletov, V. N.; Maiorova, E. D. *Russ. Chem. Bull.* **1999**, *48*, 367.

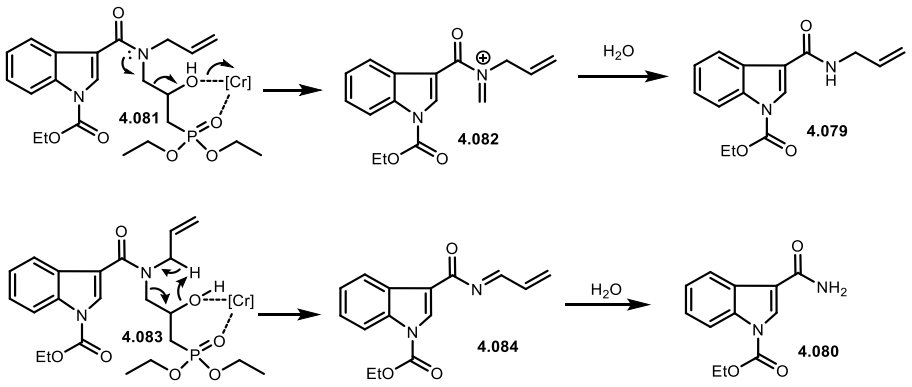
Oxidation of secondary alcohol **4.077** to ketone **4.078** was conducted under various conditions such as Swern[8], Dess-Martin[9], Parikh-Doering[10], PCC[11], bleach, Corey-Kim[12], Pfitzner-Moffatt[13], copper oxidation[14], … Only PCC gave a non-reproducible 50 % yield of ketone **4.078** as well as two side products **4.079** and **4.080** (Scheme 30).



Scheme 30: Oxidation of alcohol 4.077

The formation of **4.079** and **4.080** could be explained by the fact that alcohol and phosphonate at those position turn the molecule into a good chelating agent for chromium in PCC. Two different degradation pathways could occur from the same system, the first **4.081** used the lone pair of nitrogen to kick out the chelating part, leading to amidium **4.082** which got hydrolysed into **4.079**. The second is an elimination of allylic hydrogen **4.083** removing the chelating function from the amide to afford **4.084** which also got hydrolysed into **4.080** (Scheme 31).

[8] Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
[9] Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
[10] Parikh, J. R.; Doering, W. V. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
[11] Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647.
[12] Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586.
[13] Pfitzner, K. E.; Moffatt, J. G. *J. Am. Chem. Soc.* **1963**, *85*, 3027.
[14] Markó, I. E.; Giles, P. R.; Tsukazaki, M.; Brown, S. M.; Urch, C. J. *Science*, **1996**, *274*, 2044.

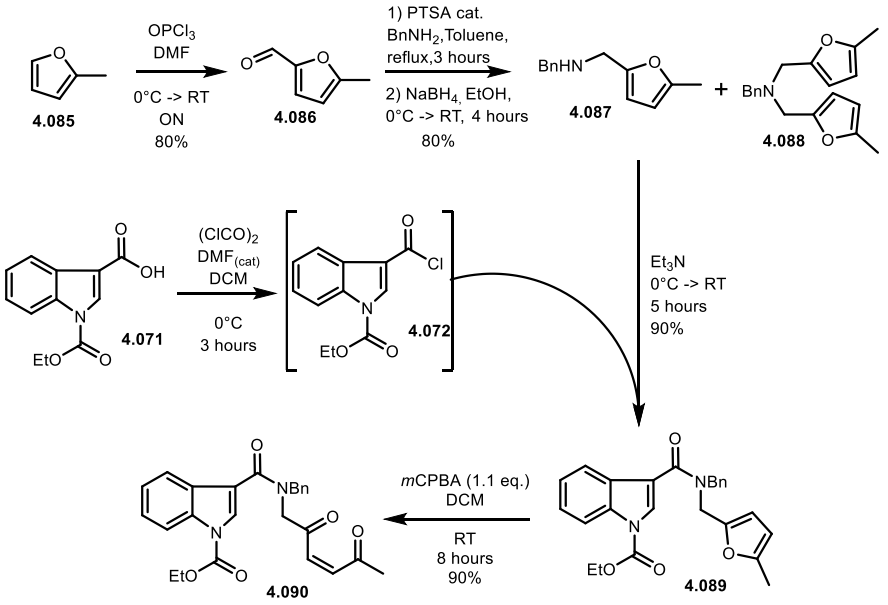


Scheme 31: Eliminations during oxidation

Because of oxidation issues, this pathway was definitely not suitable for the synthesis.

6. Synthesis of Ene-dione by *m*CPBA and Br_2

With the amide and carbamate in place, the Oxidative-Ring-Opening (ORO) of furan is available. This pathway starts with a Vilsmeier-Haack reaction on 2-methyl-furan **4.085** into **4.086** [15], followed by reductive amination of benzylamine to bring forth the secondary amine **4.087**[16], and the major side product **4.088**[17] resulting from double addition. Activation of the acid **4.071** with oxalyl chloride to the acyl chloride **4.072** and coupling with our newly formed amine **4.087** afforded **4.089** in 90 % yield. Furan **4.089** was oxidized to *Z*-ene-dione **4.090** with *m*CPBA in an excellent yield of 90 % (Scheme 32).

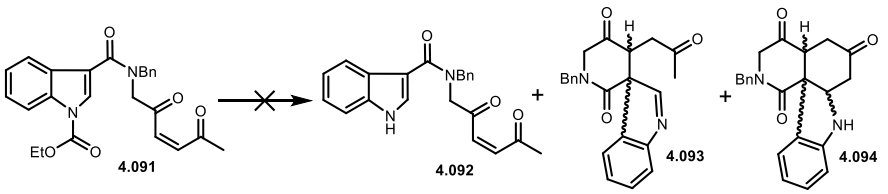


Scheme 32: First synthesis of ene-dione

The deprotection-cyclization was tested as a one-pot procedure with lithium hydroxide in H_2O and THF. Different products were expected from

[15] Semple, J. E.; Wang, P. C.; Lysenko, Z.; Jouillé, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505.
[16] Heaney, H.; Papageorgiou, G. *Tetrahedron*, **1996**, *52*, 3473.
[17] Holdren, R. F.; Hixon, R. M. *J. Am. Chem. Soc*. **1946**, *68*, 1198.

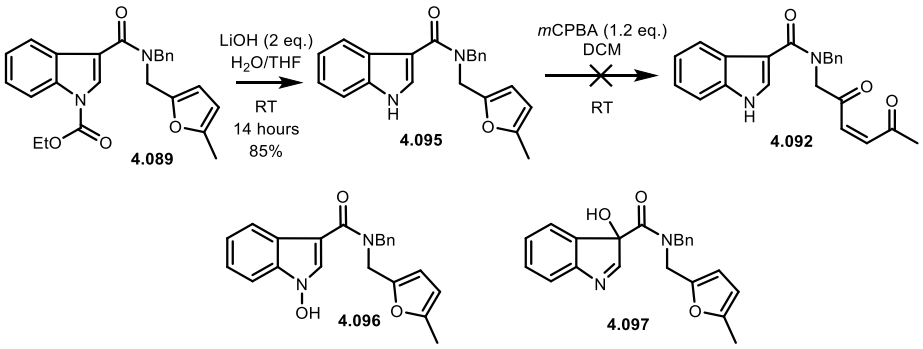
this reaction: the deprotected adduct **4.092**, the first cyclization **4.093** and the tetracyclic **4.094**. Unfortunately, only degradation was obtained (Scheme 33).



Tested conditions: **A** = LiOH (1.2eq.) in H_2O/THF, **B** = K_2CO_3 (1.2eq.) in H_2O/THF, **C** = $NaHCO_3$ (1.2eq.) in H_2O/DCM, **D** = K_2CO_3 (1.2eq.) in MeOH, **E** = Na_2CO_3 (1.2 eq.) in MeOH, **F** = DBU (1.2 eq.) in H2O/MeOH.

Scheme 33: Deprotection and cyclization

Deprotection of **4.089** prior to oxidation was also tested. The use of lithium hydroxide in aqueous tetrahydrofuran was efficient to convert **4.089** into free indole **4.095**. Unfortunately, the ensuing oxidation provided a complex mixture of compounds such as **4.096** and **4.097** (Scheme 34).

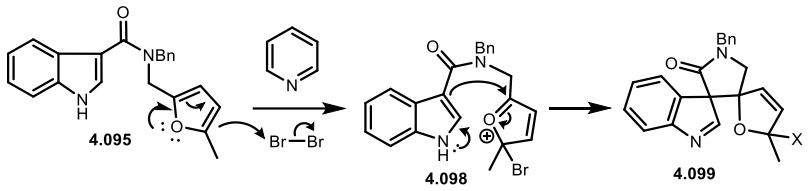


Scheme 34: Oxidation of furan 4.095

A replacement for *m*CPBA as oxidant could be bromine [18]; this reaction led to a mixture of products. Furan in **4.095** could react with bromine leading to **4.098** followed by nucleophilic attack of indole on furanoxonium leading to bi-spiro compound **4.099** which could undergo

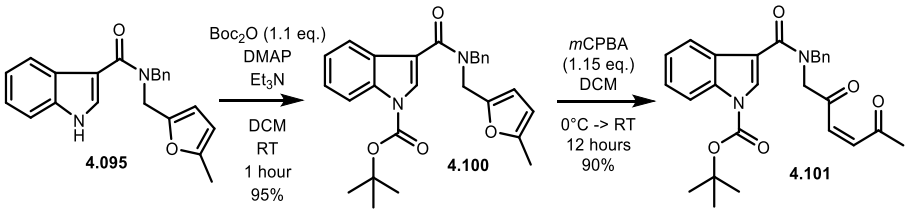
[18] Pikul, S.; Raczko, J.; Ankner, K.; Jurczak, J. *J. Am. Chem. Soc.*, **1987**, *109*, 3981.

many degradations such as hydrolysis of indolenine, hydrolysis of bromo-furan, and various 1,2 carbon shift, … (Scheme 35).



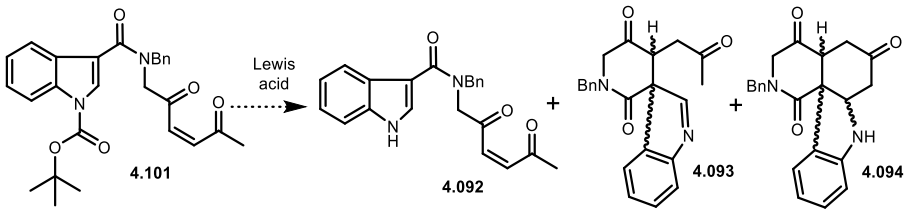
Scheme 35: Reaction with Bromine

The last tests bring to evidence that protection of indole is therefore mandatory if we want to successfully oxidize the furan. Since deprotection in basic media gave rise to problems, a Boc and acidic deprotection should solve this drawback. Protection and oxidation of **4.095** to ene-dione **4.101** was carried out without issue in excellent yield (Scheme 36).



Scheme 36: Boc protection and oxidation

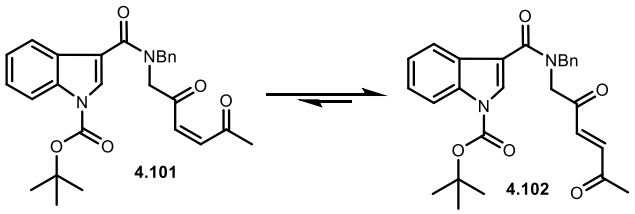
Many Lewis and Brønsted acid were tested for Boc deprotection, bidentate Lewis acid could also activate the ene-dione **4.101** into a polycyclization mechanism (Scheme 37) and (Table 1).



Scheme 37: Lewis acid cyclization

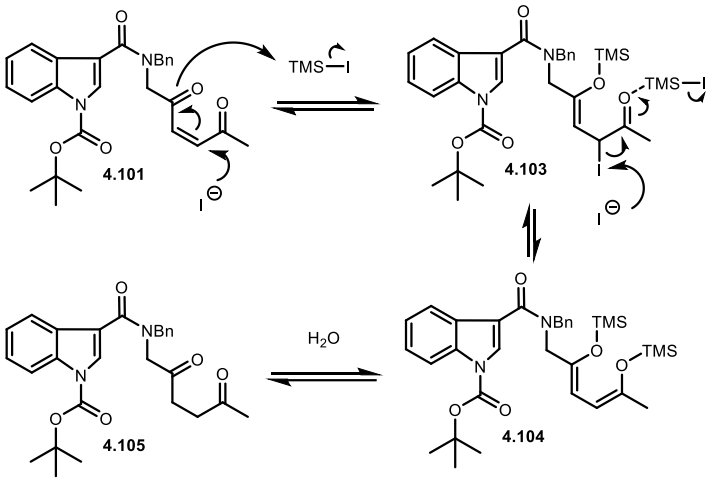
Entry	Acid	Solvent	Results
1	$Mg(OTf)_2$	DCM or THF	Isomerisation *Z*-**4.101** -> *E*-**4.102**
2	$ZnBr_2$	DCM or THF	Isomerisation *Z*-**4.101** -> *E*-**4.102**
3	$Zn(OTf)_2$	DCM or THF	Isomerisation *Z*-**4.101** -> *E*-**4.102**
4	$BF_3.OEt_2$	THF	Degradation
5	$AlMe_3$	THF	Degradation
6	TMSI	CH_3CN	Diketone **4.105**
7	TMSOTf	DCM	Isomerisation *Z*-**4.101** -> *E*-**4.102**
8	TFA	DCM	Isomerisation *Z*-**4.101** -> *E*-**4.102**
9	TFA + HCl	DCM	Isomerisation *Z*-**4.101** -> *E*-**4.102**
10	TFA + HBr	DCM	Isomerisation *Z*-**4.101** -> *E*-**4.102**

Table 1: Boc deprotection and potent cyclization



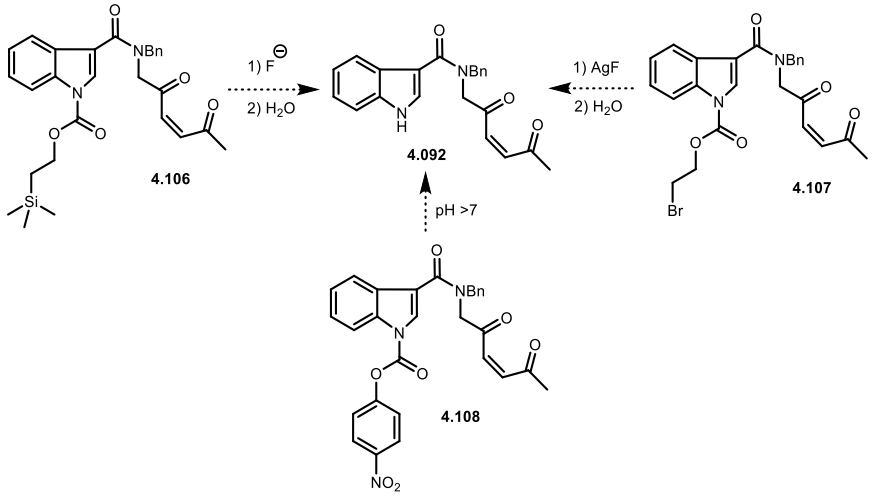
Scheme 38: Isomerisation *Z*-*E*

Most entries (1, 2, 3, 7, 8, 9, 10) afforded the *E*-**4.102** isomer without any deprotection of Boc. Boron trifluoride and trimethylaluminum led to degradation and trimethylsilyliodide furnished the diketone **4.105**, probably by activation of ene-dione **4.101** followed by Michael addition of iodide. The second ketone could be activated, and iodide can do iodine elimination leading to bis-enol **4.104** which could be hydrolysed into diketone **4.105**. This mechanism is supported by the presence of iodine in the media at the end of the reaction (Scheme 39).



Scheme 39: Reduction of ene-dione to diketone 4.105

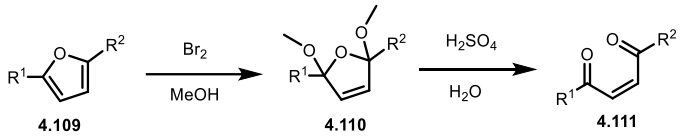
At this stage of the project, it was mandatory to find a way to deprotect indole or ene-dione without destroying the sensitive molecule. We decided to reinvestigate protecting groups and focused on entities such as Teoc **4.106**, bromoethanecarbamate **4.107** and *p*-nitrophenolcarbamate **4.108** (Scheme 40).



Scheme 40: Several protecting groups

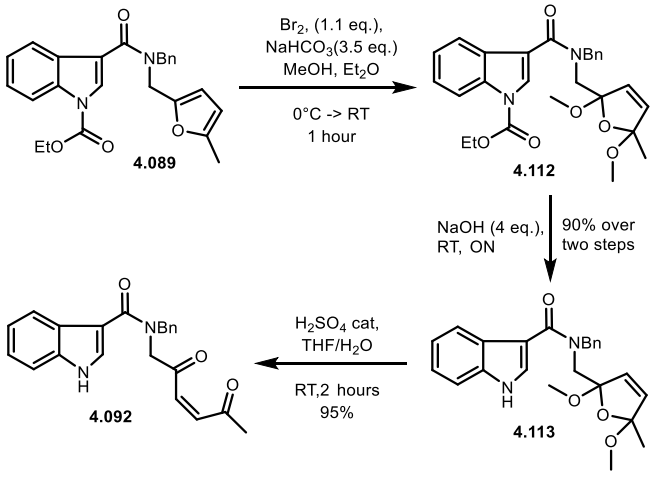
7. Synthesis of Ene-dione using bromine

Another possibility is the use of bromine in methanol to oxidize **4.109** into dimethoxy-furan **4.110**, which could get smoothly hydrolysed into ene-dione **4.111** (Scheme 41).[19]



Scheme 41: Oxidation with bromine in methanol

This procedure was tested on furan **4.089** and was successful. However, the presence of rotamers of amide and carbamate in addition to diastereoisomer of dihydrofuran makes it hard to analyse. Dimethoxy-furan **4.112** was directly deprotected by addition of sodium hydroxide in the methanolic reaction into **4.113** which was smoothly hydrolysed to indole-ene-dione *Z*-**4.092** (Scheme 42).

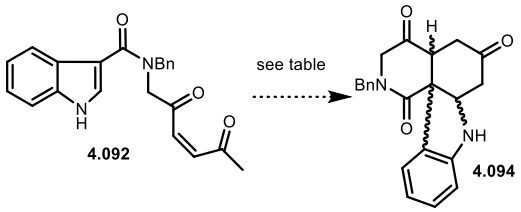


Scheme 42: Synthesis of indole-ene-dione

[19] Al-Busafi, S.; Doncaster, J. R.; Drew, M. G. B.; Regan, A. C.; Whitehead R. C. *J. Chem. Soc.*, *Perkin Trans I*, **2002**, 476.

8. Polycyclization tests

From this point, the stage was finally set for polycyclization conditions to be investigated. Ene-dione **4.092** is presumably more reactive than any precursor from the previous generation of anionic polycyclization, which were acrylate and enone derivatives. This statement makes the use of strong base useless and allowed us to test weak bases first in order to install the tetracycle **4.114** (Scheme 43) and (Table 2).



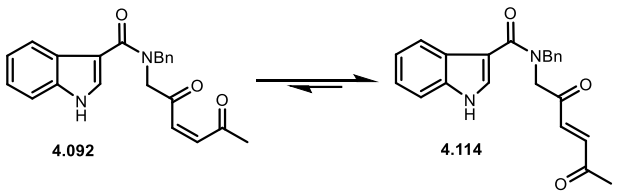
Scheme 43: Cyclization to tetracycle 4.094

Entry	Base	Solvent	T°	Outcome
1	Pyridine	DCM	RT	Isomerisation *Z*-**4.092** -> *E*-**4.114**
		THF	0°C	Isomerisation *Z*-**4.092** -> *E*-**4.114**
		CH_3CN	0°C	Isomerisation *Z*-**4.092** -> *E*-**4.114**
2	2,6-lutidine	DCM	0°C	Isomerisation *Z*-**4.092** -> *E*-**4.114**
		THF	0°C	Isomerisation *Z*-**4.092** -> *E*-**4.114**
		CH_3CN	0°C	Isomerisation *Z*-**4.092** -> *E*-**4.114**
3	DMAP	DCM	0°C	Degradation
		THF	0°C	Isomerisation *Z*-**4.092** -> *E*-**4.114**
		CH_3CN	0°C	Isomerisation *Z*-**4.092** -> *E*-**4.114**
4	Et_3N	DCM	0°C	Degradation
		THF/H_2O	RT	Isomerisation *Z*-**4.092** -> *E*-**4.114**
		CH_3CN	RT	Degradation
5	DABCO	DCM	0°C	Degradation
		THF	0°C	Degradation

		CH_3CN	0°C	Degradation
6	DIPEA	DCM	RT	Isomerisation *Z*-**4.092** -> *E*-**4.114**
		THF	RT	Isomerisation *Z*-**4.092** -> *E*-**4.114**
		CH_3CN	RT	Isomerisation *Z*-**4.092** -> *E*-**4.114**
7	Morpholine	DCM	0°C	Degradation
		THF	0°C	Degradation
		CH_3CN	0°C	Degradation
8	NMM	DCM	0°C	Degradation
		THF	RT	Degradation
		CH_3CN	0°C	Degradation
9	DBU	DCM	0°C	Degradation
		THF	RT	Degradation
		CH_3CN	0°C	Degradation
10	TMG	DCM	0°C	Degradation
		THF	0°C	Degradation
		CH_3CN	0°C	Degradation

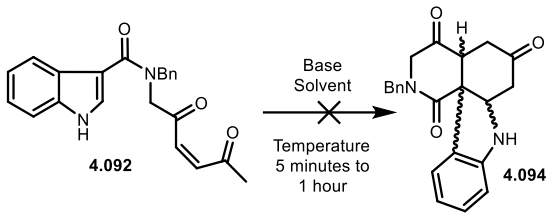
Table 2: Cyclization with weak bases

Unfortunately, degradation and isomerisation are the only two types of observed outcomes. This is further evidence for our previous statement, ene-dione **4.092** is highly reactive. Entry **9** and **10** were misfortune, both are on the pK_a range of indole and we naively expected interesting results. But maybe it could be solved with an inorganic base or a strong organic base which would do a total deprotonation instead of equilibrium (Scheme 44).



Scheme 44: Isomerisation *Z-E*

Polycyclization tests with stronger bases were performed (Scheme 45).

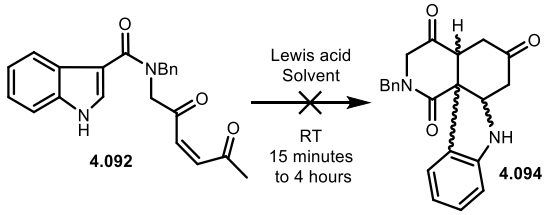


Tested conditions: **A** = 1 eq. *n*BuLi, THF, -78°C; **B** = 1 eq. NaHMDS, THF, -78°C;
C = 1 eq. KHMDS, THF, -78°C; **D** = 1 eq. LDA, THF, -78°C;
E = 0.25 eq. LiOH, THF, H_2O, 0°C; **F** = 0.25 eq. NaOH, THF, H_2O, 0°C;
G = 0.25 eq. KOH, iPrOH, -40°C; **H** = 0.25 eq. KOH, THF, H_2O, 0°C;
I = 0.25 *t*BuOK, THF, 0°C; **J** = *t*BuOK, Toluene, 0°C.

Scheme 45: Cyclization with strong bases

Degradation was the only outcome obtain with strong bases. The molecule is definitely too sensitive to weak or strong bases.

Unsuccessful with bases, acid catalytic tests were performed. Both Brønsted and Lewis acids were used (Scheme 46).



Tested conditions: **A** = 1.2 eq. $Mg(OTf)_2$ in DCM or THF;
B = 1.2 eq. $ZnBr_2$ in DCM or THF; **C** = 1.2 eq. $Zn(OTf)_2$ in DCM or THF;
D = 1.2 eq. $ZnCl_2$ in DCM or THF; **E** = 0.1 eq. PPTS in DCM or THF;
F = 0.05 eq. PTSA in DCM or THF; **G** = 0.05 eq. CSA in DCM or THF;
H = 1 eq. TFA in DCM; **I** = 0.05 eq. HCl in DCM; **J** = 0.05 eq. HBr in DCM.

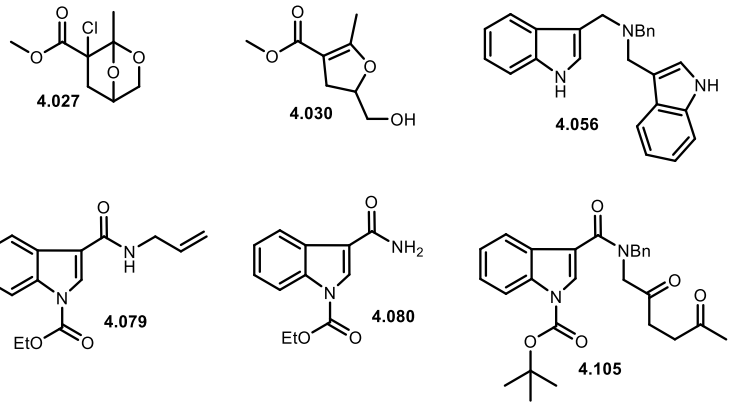
Scheme 46: Cyclization with acids

Isomerisation to *E*-ene-dione **4.114** was the only outcome except with PPTS which provide back the starting material. According to these data strong inorganic acid can do the isomerisation. Therefore, the isomerisation with metallic Lewis acid is probably due to traces of Brønsted acid.

So far, no cyclized product **4.094** could be synthetized.

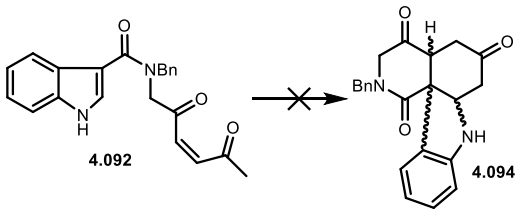
9. Conclusions

Different pathways were used to reach our polycyclization precursors, all along the synthesis was adapted to avoid the detected side products, such as **4.027**, **4.030**, **4.056**, **4.079**, **4.080** and **4.105** (Scheme 47).



Scheme 47: Example of side products

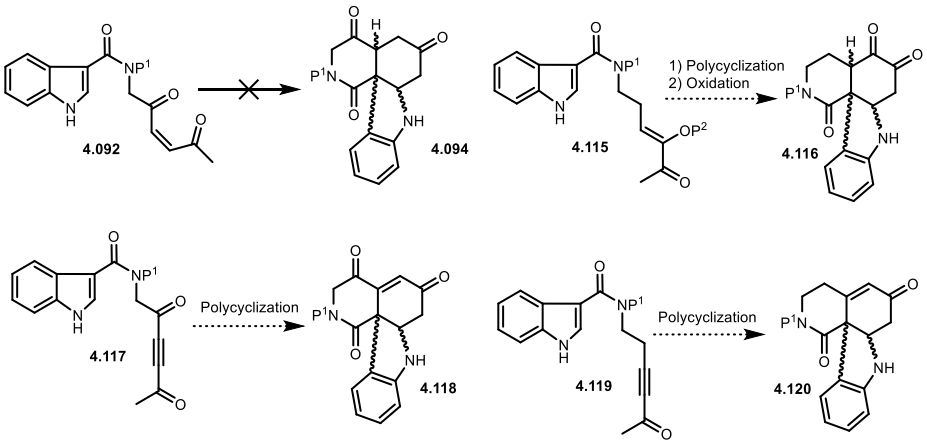
Finally, the desired precursor **4.092** was synthetized, however no conditions could cyclize it into the tetracycle **4.094**. The high reactivity of the ene-dione moiety appears to be problematic (Scheme 48).



Scheme 48: precursor and target molecule

10. Perspectives

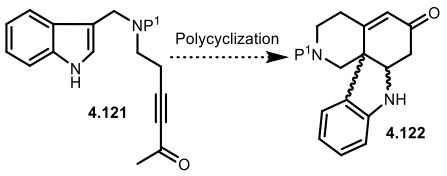
Because of the failure to cyclize ene-dione **4.092** into the desired tetracycles **4.094**, we considered alternatives to obtain similar products **4.116**, **4.118** or **4.120** with **4.115**, **4.117** and **4.119** as precursors, respectively (Scheme 49).



Scheme 49: Alternatives

Precursor **4.119** looks more promising than **4.115** and **4.117**. Simple ynone **4.119** could be easy solution if we find a way to reduce the unsaturation from the α-face. The yne-dione **4.117** would probably afford the same difficulties and issues as our ene-dione **4.092**. Discrimination between the ketones in diketone **4.116** will increase the difficulty of the next steps.

The second part of those perspectives is the presence of the amide to avoid ammonium elimination. This carbonyl most probably changes the total chemistry of the molecule, just to prevent few percent of side products. The synthesis of the next precursors **4.121** will be tested without the amide. If a major issue is encountered, it will be set back (Scheme 50).



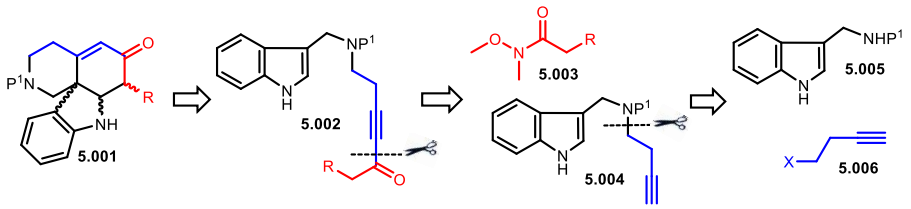
Scheme 50: Future attempts

Chapter V

Third Generation Anionic Polycyclization

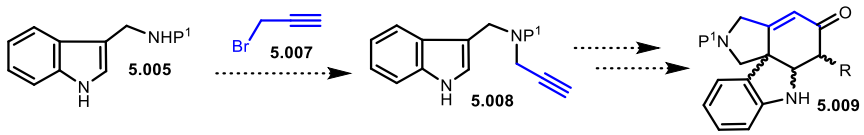
1. Ynone synthesis and preliminary tests

As already mentioned in Chapter IV, **5.001** was assigned as a strategic target being derived from intermediate **5.002** upon polycyclization. The disconnection we envisioned is based on the mono addition of a double anion of **5.004** on Weinreb amide **5.003** (in red). Finally, the amine **5.004** ought to be an S_N2 product between amine **5.005** and homo-propargylic moiety **5.006** (in blue) (Scheme 1).



Scheme 1: Disconnection for 5.002 as precursor

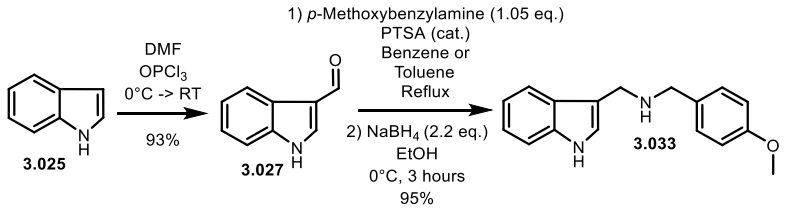
Due to the potential problems that might arise, a model study was planned. The use of commercially available and more reactive propargyl bromide **5.007** was considered instead of **5.006**. The S_N2 reaction of amine **5.005** with propargyl bromide **5.007** (in blue) should lead to **5.008**. The [5,6] tetracycle **5.009** should be derived as the polycyclization product with **5.008** as starting material (Scheme 2).



Scheme 2: Use of propargyl bromide

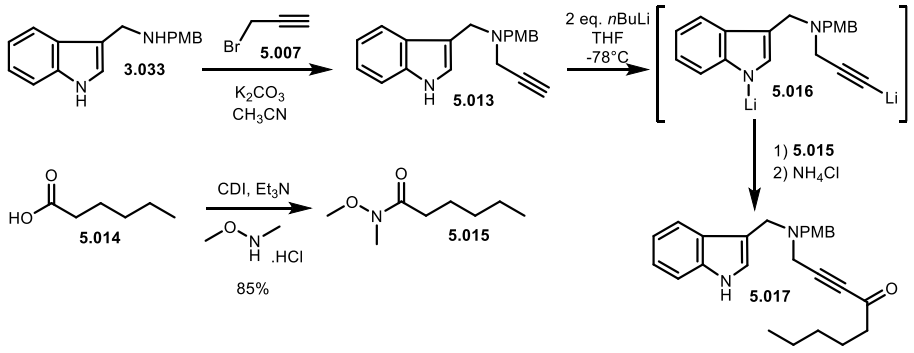
a. Synthesis of precursor

The synthesis starts with Vilsmeier-Haack reaction of indole **3.025** to bring forth formyl-indole **3.027**[1], that is directly submitted to a reductive amination with *p*-methoxy-benzylamine and sodium borohydride to install secondary amine **3.033** (Scheme 3).



Scheme 3: Synthesis of amine 3.033

Amine **3.033** was conveniently propargylated with **5.007** to form **5.013**. The Weinreb amide **5.015** was produced by condensation of hexanoic acid **5.014** and *N,O*-dimethylhydroxyamine. The double anion **5.016** was obtained by reaction of propagylamine **5.013** and two equivalents of *n*-butyllithium. Weinreb amide **5.015** was then added to the double anion **5.016** and the mixture was quenched with a saturated aqueous solution of NH_4Cl. The ynone **5.017** was obtained as planned with a small quantity of side-products. Unfortunately, the ynone **5.017** is unstable on silica gel (even neutralised with triethylamine) (Scheme 4).

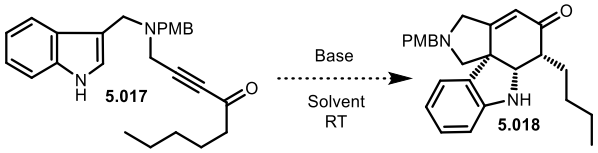


Scheme 4: Synthesis of ynone 5.017

[1] Smith, G. F. *J. Chem. Soc.* **1954**, 3842.

b. Polycyclization tests

With ynone **5.017** in hand, different bases were tested to forge tetracycle **5.018** (Scheme 5) and (Table 1).

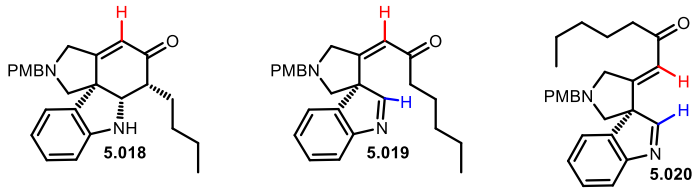


Scheme 5: Polycyclization of ynone

Entry	Base (eq.)	Solvent	Outcome
1	*t*BuOK (0.25)	THF	Degradation
2	*t*BuOK (0.25)	CH_3CN	Degradation
3	DBU (0.40)	THF	New products
4	DBU (0.40)	CH_3CN	New products
5	DIPEA (0.40)	DCM	Starting material

Table 1: Polycyclization conditions

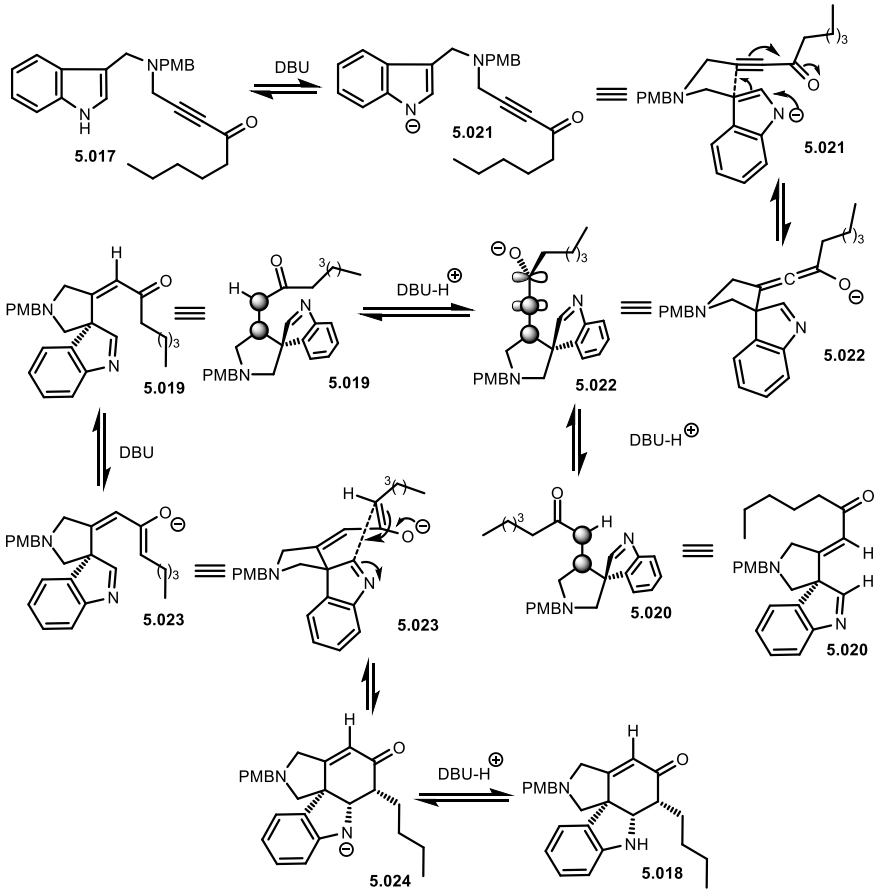
Entries 1 and 2 reveal that potassium *tert*-butoxide lead to degradation in THF or in CH_3CN. Entry 5 shows that DIPEA does not promote the formation of any new product. As shown in entries 3 and 4, DBU furnishes several products which could be a mixture of **5.019**, **5.020** or **5.018**. The vinylic hydrogen (in red) possesses a characteristic shift in NMR, three new peaks were observed between 5,5 ppm and 6,5 ppm. Finally, the indolenine hydrogen (in blue) possesses the same feature with a chemical shift between 8 and 8,5 ppm and two new peaks were observed. Purification provides a product which could be the tetracycle **5.018** (Scheme 6).



Scheme 6: Potential products of cyclization

c. Postulated mechanism

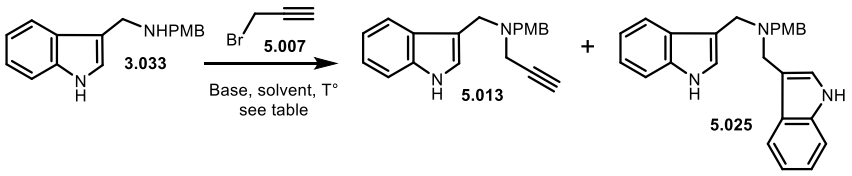
Since the initial tests showed some priming results, we decided to propose a mechanism based on the data we obtained. Indole **5.017** was deprotonated with DBU to give **5.021** which can undergo a Michael addition in a 5-*exo*-*dig* fashion to **5.022** (and its isomer with the side chain down and alkoxide up). Reprotonation of **5.022** with DBU-H$^+$ would give *cis*-**5.020** or *trans*-**5.019**. Enone **5.019** could be deprotonated by DBU into enolate **5.023** which would perform a 6-*exo*-*trig* cyclization on the indolenine moiety to yield **5.024**. Finally, in our mechanistic proposal **5.024** would be reprotonated into our target molecule **5.018** (Scheme 7).



Scheme 7: Proposed mechanism for polycyclization

2. Improvement of synthesis

Propargylation of amine **3.033** leads to two main products, namely **5.013** and bis-indole **5.025** (Scheme 8) and (Table 2).



Scheme 8: Propargylation of amine 3.033

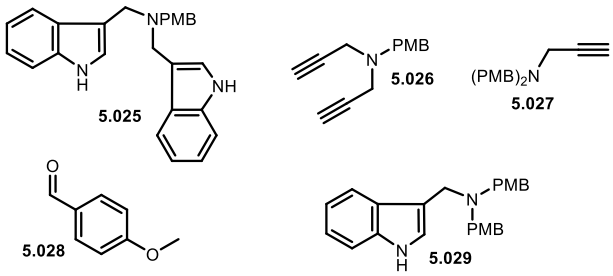
Entry	Solvent	Base (eq.)	T (°C)	5.013 (%)	5.025 (%)
1	THF	K_2CO_3 (1.2)	20	68	10
2	THF	K_2CO_3 (1.2)	0	72	10
3	CH_3CN	K_2CO_3 (1.2)	20	80	5
4	CH_3CN	K_2CO_3 (1.2)	0	85	5
5	CH_3CN	K_2CO_3 (3)	20	85	5
6	CH_3CN	Na_2CO_3 (3)	20	80	5
7	CH_3CN	Cs_2CO_3 (3)	20	40	20
8	CH_3CN	DIPEA (1.2)	20	50	20
9	DCM	DIPEA (1.2)	20	75	10
10	DCM	DBU (1.2)	20	70	10

Table 2: Conditions for propargylation

Most of the entries (1, 2, 3, 6, and 9) provide a proper yield of the target product **5.013**. The best conditions are summarized in entries 4 and 5 with an excess of K_2CO_3 at 0°C or ambient temperate to furnish 85 % of the target and around 5 % of bis-indole **5.025**. Slightly stronger bases (7 and 10) did not improve the outcome of the reaction.

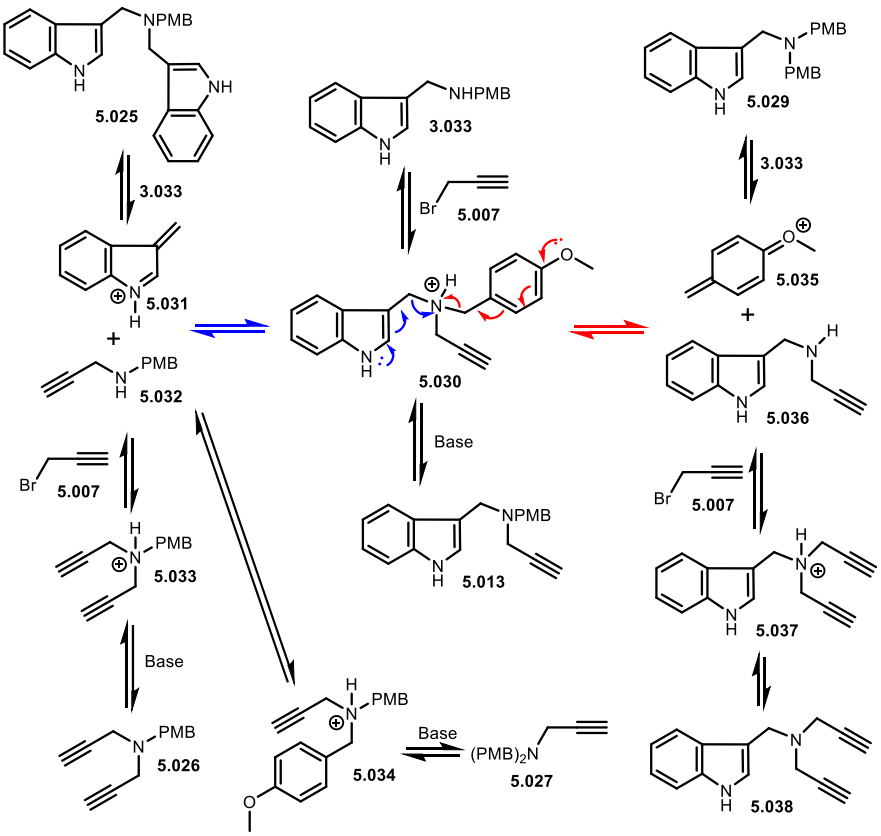
In addition to bis-indole **5.025**, several other side-products were isolated such as bis-propargylamine **5.026**, tertiary amine **5.027**,

anisaldehyde **5.028** (0.05 %) and finally, **5.029** which was observed by mass spectrometry (Scheme 9).



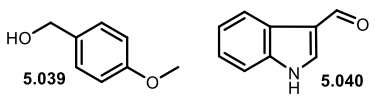
Scheme 9: Side-products

A proposed mechanism to explain their presence of these side-products is discussed in this paragraph. Propargylation of amine **3.033** leads to ammonium ion **5.030**. This ammonium **5.030** could undergo three reactions, first deprotonation towards the desired molecule **5.013**, the second (in blue) fragments into ene-indoleninium **5.031** and amine **5.032** and the third (in red) fragments into oxonium **5.035** and amine **5.036**. Addition of amine **3.033** on ene-indoleninium **5.031** affords the main side product bis-indole **5.025**. Propargylation of amine **5.032** furnishes **5.026** after deprotonation. The same amine **5.032** could also react with the oxonium **5.035** to forge the tertiary amine **5.027** after deprotonation. Addition of amine **3.033** on oxonium **5.035** affords tertiary amine **5.029**. Finally, the speculated secondary amine **5.036** undergoes propargylation and deprotonation into **5.038** (Scheme 10).



Scheme 10: Mechanism under propargylation

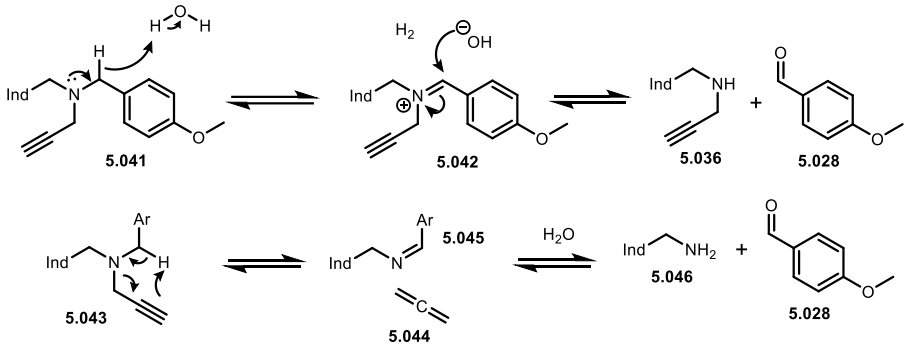
The isolation of anisaldehyde **5.028** was a surprise as no anisyl alcohol **5.039** or indole 3-carbaldehyde **5.040** were observed. Absence of those products promotes a different pathway than addition of water on oxonium **5.035** toward alcohol **5.039** then oxidation by air to anisaldehyde **5.028** (Scheme 11).



Scheme 11: Unobserved side-products

The formation of such a small quantity of anisaldehyde **5.028** could come from high energy processes, we speculated two hypothetical mechanisms. First, hydride elimination from the main product **5.041** and

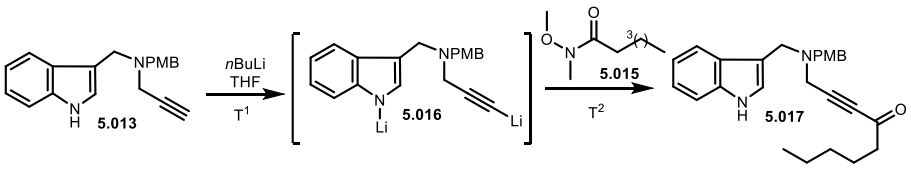
reduction of water (always present in acetonitrile) to form the iminium salt **5.042** which could react to provide anisaldehyde **5.028** and secondary amine **5.036**. The second option could be a Cope-like [2] rearrangement **5.043** furnishing imine **5.045** and allene **5.044**. Hydrolysis of the imine **5.045** could provide primary amine **5.046** and the desired anisaldehyde **5.028** (Scheme 12).



Scheme 12: Potential anisaldehyde 5.028 formation

Luckily, the formation of the ynone **5.017** from the corresponding Weinreb amide **5.015** was much easier to optimize. The double deprotonation of **5.013** in the presence of *n*BuLi is instantaneous and can be followed visually since the lithium-indole is green, and the bis-metallated species **5.016** is pink. As might be expected, the second deprotonation is not complete at -78°C and higher temperatures are required to fully convert the material into the desired product. The completion with one equivalent of Weinreb amide **5.015** is impossible, and a small excess is needed. The addition reaction takes place between -20°C and room temperature. No addition on indole-lithium anion were observed. The resulting mixture was purred on Et_2O and a saturated aqueous solution of NH_4Cl, any other work-up resulted in a loss of target product (Scheme 13) and (Table 3).

[2] Szabó, A.; Hermecz, I. *J. Org. Chem*. **2001**, *66*, 7219.

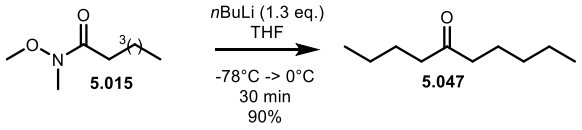


Scheme 13: Double anion chemistry

Entry	T^1 (°C)	5.015 (eq.)	T^2 (°C)	Outcome
1	-78	1	-78°C to 0	Not full conversion
2	-78 to 0	1	-78°C to 0	Not full conversion
3	-78 to 0	1.3	-78°C to 0	Not full conversion
4	-78 to 0	1.3	-78°C to 20	Full conversion, 85 % yield

Table 3: Optimisation of double anion chemistry

Even with a full conversion of the starting material **5.013** and an approximate yield of 85 %, the purification of ynone **5.017** was problematic. The excess of Weinreb amide **5.015** is a solution for the conversion but an issue for the purification. Indeed, the addition of the slight excess of *n*BuLi on Weinreb amide **5.015** furnished decanone **5.047.** This speculation was tested on the reaction conditions and provide an excellent yield of **5.047** (Scheme 14).



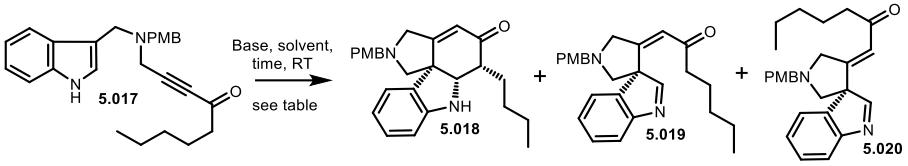
Scheme 14: Addition of *n*BuLi on Weinreb amide

The two products **5.015** and **5.047** could be a main issue for the polycyclization because these substrates are prone to enolization in the presence of base. Since ynone **5.017** appears to be extremely reactive on many supports as uncontrolled intramolecular and intermolecular reactions happened on silica, neutralised silica, alumina, and florisil. A simple way to separate the polar and non-polar materials was offered by the partitioning between acetonitrile and petroleum ether. Acetonitrile and *n*-hexane was proven to be the best combination for this and removed all undesired

decanone **5.047** and most of Weinreb amide **5.015** in the hexane phase. The product obtained was considered pure enough for polycyclization tests and the same procedure could be repeated.

3. Third Generation Anionic Polycyclization (TGAP)

Polycyclization with DBU was reproduced and followed by few solvent tests (Scheme 15) and (Table 4).



Scheme 15: Polycyclization with DBU and TMG

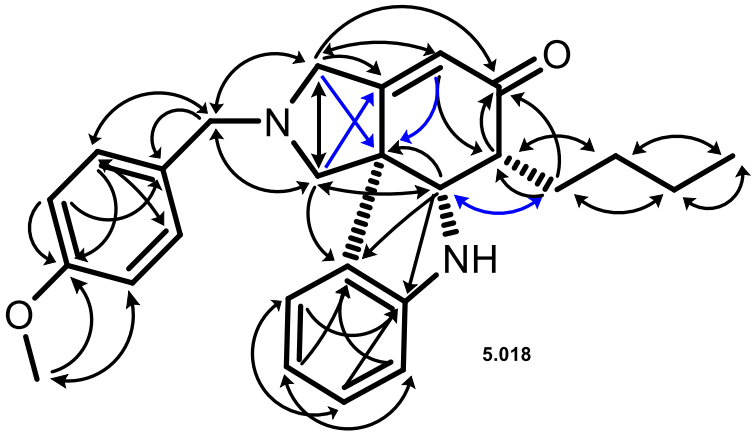
Entry	Base (0.2 eq.)	Solvent	Time	5.017 (%)	5.018 (%)	5.019 (%)	5.020 (%)
1	DBU	CH_3CN	10 min	30	5	40	25
2	DBU	CH_3CN	1h	15	15	40	25
3	DBU	CH_3CN	3h	/	30	35	25
4	TMG	CH_3CN	1h	50	/	30	15
5	TMG	CH_3CN	3h	30	/	40	20
6	DBU	DCM	24h	/	20	/	30
7	DBU	Benzene	20h	/	20	/	40
8	TMG	Benzene	20h	30	/	/	50
9	DBU	THF	18h	/	40	10	5
10	DBU	THF	42h	/	50	/	5

Table 4: Polycyclization conditions

In every reaction *cis*-**5.020** could be observed. In most of the case a 2:1 ratio can be observed between *trans*-**5.019** and *cis*-**5.020** (entries 1, 2, 3, 4, 5 and 9). As such, the reprotonation step exhibits a facial selectivity of 2:1 in acetonitrile and tetrahydrofuran. Concerning entry 8, only *cis*-**5.020** was detected in benzene with tetramethylguanidine (TMG). In entries 4, 5 and 8 no product was observed, this is probably because TMG is basic enough to deprotonate indole but not basic enough to the second deprotonation in those conditions. The use of DBU in acetonitrile and tetrahydrofuran is

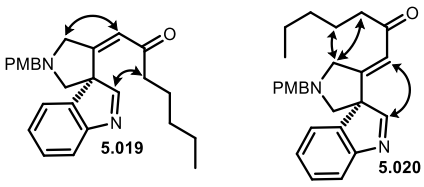
promising (entries 1, 2, 3, 9 and 10) with so far, a yield of 50 % into our target molecule **5.018** in tetrahydrofuran in for 42 hours and a potential conversion of 65 % in acetonitrile.

With enough material available, the structures of the main product and intermediate could be analytically verified by two-dimensional NMR. All the arrows represent observed HMBC correlation inside our target tetracycle **5.018** and the blue arrows confirm the newly formed vicinity of some carbons in the scaffold (Scheme 16).



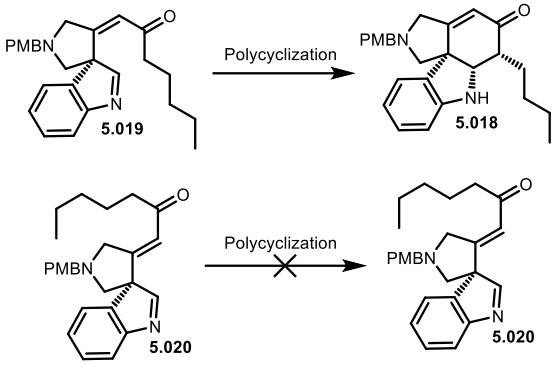
Scheme 16: HMBC correlations of tetracycle

The difference between *trans*-**5.019** and *cis*-**5.020** was made through NOESY correlations. Purification appears problematic as **5.019** convert into **5.020** on triethylamine neutralised silica and both partially decompose in the process (similar interactions were removed for the simplicity of understanding) (Scheme 17).



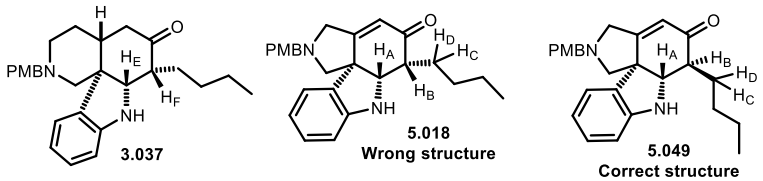
Scheme 17: NOESY correlations

As simple NOE is not enough to confirm the structure of both intermediates. Both underwent the polycyclization conditions and only **5.019** cyclized (Scheme 18).



Scheme 18: Cyclization of intermediates

However, the following error occurred. Since at the beginning we expected to create **5.018** with diastereoselectivities similar to those in **3.037**. However, H_B is a double triplet (as expected by NMR) with coupling constants of 9.6 Hz, 4.8 Hz and 4.8 Hz. The rotation freedom of the side chain should make H_C and H_D identical from the point of view of H_B (4.8 Hz looks normal). A 9.6 Hz constant in a 6 membered ring implies an *anti*-relationship between H_A and H_B and of course the other stereochemistry for the side chain. To improve the viability of this statement the coupling constant between H_E and H_F in **3.037** is 3.3 Hz for a *syn*-relationship. From now on we will consider **5.049** as our major product and **5.018** as a potential minor diastereoisomer. The fact that **5.049** is our major product is a tremendously good new, as it possesses 3 chiral centres which are identical to those in manzamine A **1.001** (Scheme 19).

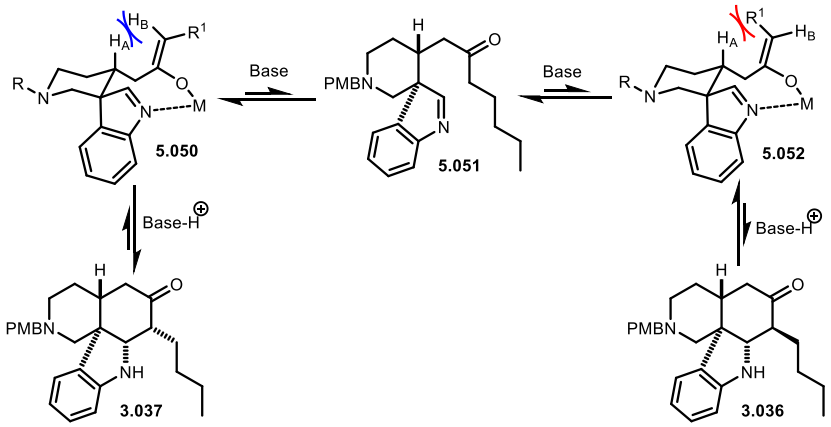


Scheme 19: Confirmation of stereochemistry

4. Mechanistical reconsiderations

To explain this variation in diastereoselectivity, we became focused to find a difference between the Second Generation Anionic Polycyclization (SGAP) and the Third Generation Anionic Polycyclization (TGAP). We thought that the final 6-*exo*-*trig* cyclization would be a good starting point.

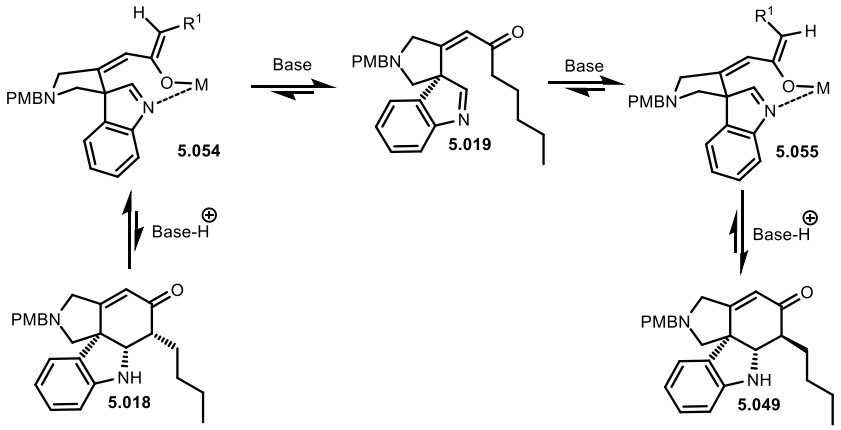
In SGAP, four possible enolates from **5.051** could be expected, however, only two of them could perform the final cyclization due to correct orbital alignments **5.050** and **5.052**. The major product **3.037** should emerge from enolate **5.050**. Steric hinderance could be observed in both enolates but R^1-H_A interaction (red) in **5.052** should make this conformation less favoured. In **5.050**, H_A-H_B interaction (blue) is smaller because both are hydrogens. It looks like the discrimination is based on steric hinderance with H_A and provides **3.037** with potential equilibria from the minor product **3.036** or minor enolate **5.052** (Scheme 20).



Scheme 20: Last steps of SGAP

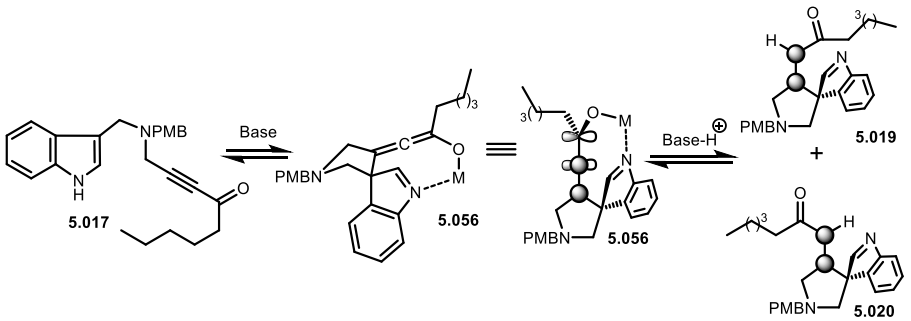
In TGAP, there are two possible enolates from **5.019**, respectively **5.054** and **5.055**. The major product **5.049** should come from enolate **5.055**. Thanks to the unsaturation, there is no hydrogen to create steric hindrance. The presence of M (DBU-H^+ in this case) induces steric hindrance with R^1 and make **5.055** the most favoured enolate. Activation due to M could be a reason why TMG is not able to cyclize at this stage. The high

diastereoselectivity of this step can be explained by potential equilibria from minor product **5.018** or minor enolate **5.054** (Scheme 21).



Scheme 21: Last steps of TGAP

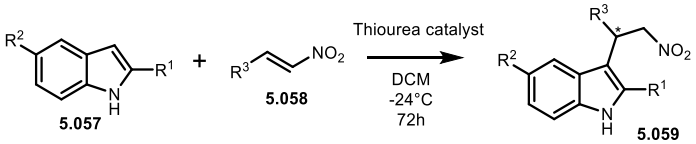
The third reconsideration is based on the reprotonation of allenolate **5.056**. If M could coordinate the indolenine moiety, the scaffold would be an 8-membered ring in **5.056**. It would rigidify the molecule skeleton and favour reprotonation towards **5.019** instead of **5.020**. The optimal solution to increase the yield would be to find an "M" which can lead only to **5.019** (Scheme 22).



Scheme 22: Reprotonation of allenolate 5.056

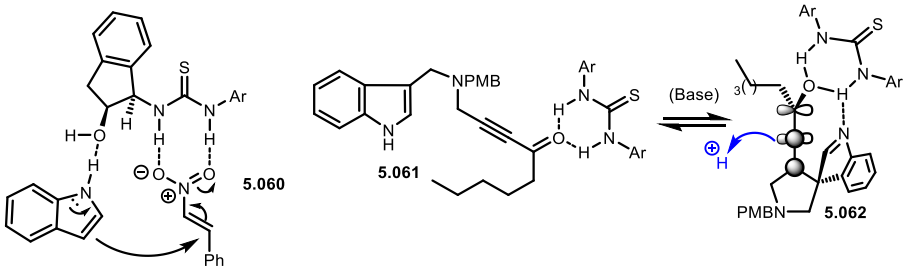
5. Organocatalysed polycyclization?

To optimise our main reaction, we wanted to find the optimal "M". Ricci *et al.* proposed the addition of indole **5.057** on nitroalkene **5.058** in the presence of thiourea derivatives as catalyst to obtain **5.059** (Scheme 23).[3]



Scheme 23: Thiourea catalyst reaction

The reaction is based on the activation of the nitro moiety with thiourea and at the same time, activation of indole by the chiral alcohol in **5.060**. Even though our system is less activated than a vinylnitro, the addition in **5.061** would be intramolecular and the sterically less demanding ynone provides more space around the carbonyl part. With the use of a weak base, the cyclized product **5.062** should be extremely stabilized and reprotonation could only occur from by the less hindered face (blue arrow) (Scheme 24).

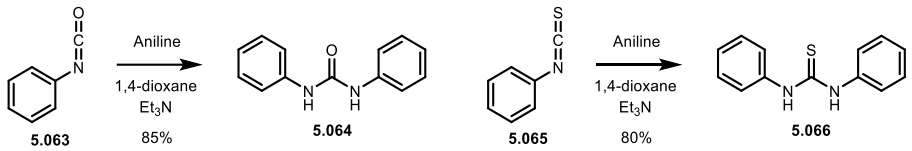


Scheme 24: Plausible activation states

The idea was tested and diphenylurea **5.064** and diphenylthiourea **5.066** were synthetized[4] (Scheme 25).

[3] Herrera, R. P.; Sgarzani, V.; Bernardi, L.; Ricci, A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6576.

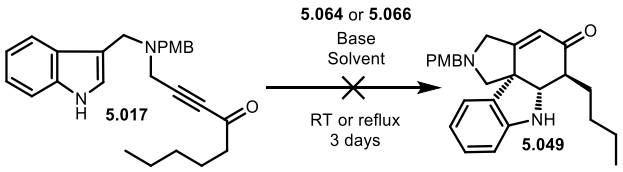
[4] Perveen, S.; Hai, S. M. A.; Khan, R. A.; Khan, K. M.; Afza, N.; Sarfaraz, T. B. *Synth. Commun.* **2005**, *35*, 1663.



5.063 **5.064** **5.065** **5.066**

Scheme 25: Syntheses of urea and thiourea derivatives

Those catalysts were applied to our polycyclization precursor (Scheme 26).



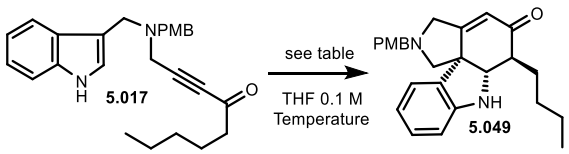
Bases: DMAP or Et_3N or Imidazole or none
Solvents: THF or CH_3CN or DCM or Benzene

Scheme 26: Organocatalysed tests

No matter the combination between the base and solvent, no reaction happened with urea or thiourea even at higher temperature than ambient temperature (higher temperatures led towards degradation of starting material). Unfortunately, it is an evidence that this organo-catalyst is not convenient for the polycyclization.

6. Polycyclization with *t*BuOK

Even after the first failures with potassium *tert*-butoxide, it could be a proper base for the TGAP as it is one of the best choices for SGAP. Softer conditions were envisioned this time. Entry 1 represents the same conditions as previously tested. Time looks like a major factor in this reaction, it appears that the product **5.037** degrades under the reaction conditions. The softer the reaction the better (entry 5). The reported reaction time for SGAP is approximately 1 hour at ambient temperature with 20 mol% of *t*BuOK at the same concentration (Scheme 27) and (Table 5).

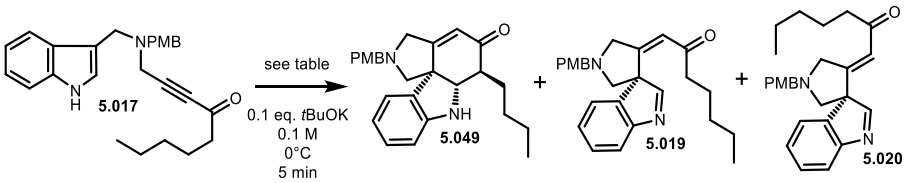


Scheme 27: TGAP with *t*BuOK

Entry	tBuOK (eq.)	T	Time	5.049 (%)	Outcomes
1	0.25	RT	30 min	/	Degradations
2	0.1	RT	30 min	10	Degradations
3	0.1	0°C	30 min	20	Degradations
4	0.1	0°C	15 min	30-35	Degradations
5	0.1	0°C	5 min	60-65	Cleaner NMR

Table 5: Conditions with *t*BuOK

After this success, we continued to investigate if potassium can be an efficient "M" for the reprotonation. Few conditions and solvents are summarized in (Scheme 28) and (Table 6).



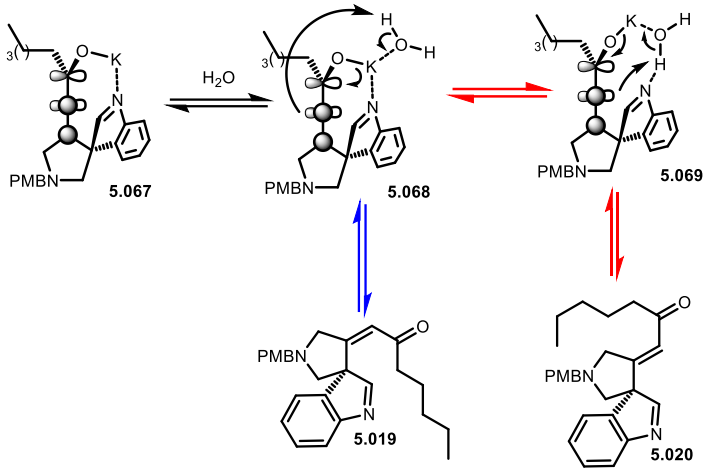
Scheme 28: Efficiency of facial reprotonation

Entry	Solvent	5.049 (%)	5.019 (%)	5.020 (%)
1	THF	65	/	/
2	CH_3CN	60	/	/
3	Toluene	/	/	65
4	Benzene	/	/	65
5	THF + 1 eq. H_2O	5	50	15

Table 6: *t*BuOK in various solvents

Potassium *tert*-butoxide exhibited a very high efficiency for the facial reprotonation, so potassium can be considered as very good "M" in tetrahydrofuran and acetonitrile (entries 1 and 2). The selectivity in aromatic solvents is also high but with inverted face-selectivity (entries 3 and 4). Water in entry 5 reduced the selectivity and slowed down the rate of the reaction. An explanation for entries 3, 4, 5 could be provided from **5.067** as potassium might form a chelated intermediate **5.067**.[5] If we add water to this compound, it will coordinate potassium then there are two options (blue and red). If the reprotonation of allenolate **5.068** happens for external face, it will furnish the desired intermediate **5.019** (in blue). On the other hand, if the water chelated adduct rearranges to allenolate **5.069**, reprotonation from the internal face is more favoured and will provide **5.020** (red). A similar mechanism could explain why toluene and benzene produce only **5.020** (red pathway with *tert*-butanol instead of water) (Scheme 29).

[5] Even if potassium is known to be mostly dissociated, there is few examples where it can be chelated or coordinated.
(a) Domingos, A. M.; Sheldrick, G. M. *Acta Cryst.* **1974**, *B30*, 517. (b) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462. (c) Tesh, K. F.; Hanusa, T. P.; Huffman, J. C. *Inorg. Chem.* **1990**, *29*, 1584.

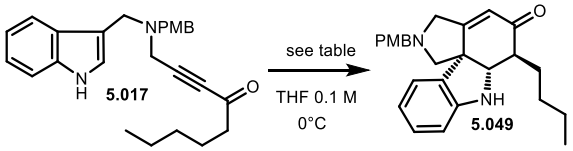


Scheme 29: Variation due to solvent

7. Optimisation of TGAP with *t*BuOK

Although 65 % yield is already very good, we were curious if a few modifications of some parameters could enhance this yield even further. As a double intramolecular cyclization, it should be sensitive to the concentration of the mixture. Time can play a major role as our product slowly degrades. Maybe the proportion of *t*BuOK is still too high and leads to decomposition of our target.

The amount of *t*BuOK was our first target for optimisation. Inconveniently, *t*BuOK has to be added as a **SOLID**, any solution will destroy the starting material even at -78°C. Slow dissolution of *t*BuOK in the mixture gave the best yield (Scheme 30) and (Table 7).



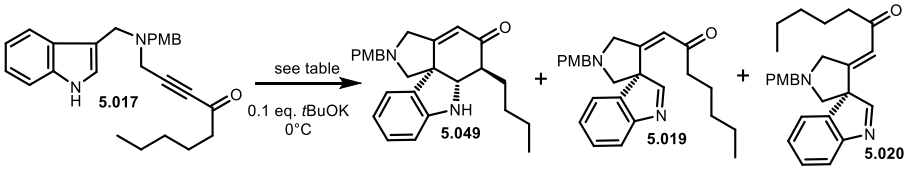
Scheme 30: Required quantity of *t*BuOK

Entry	*t*BuOK (%)	5.049 (%)	Comments
1	10	60-65	Standard
2	5	55	Messier than Entry 1
3	2	/	Starting material
4	1	/	Starting material
5	0.5	/	Starting material

Table 7: Required quantity of *t*BuOK

Entries 3, 4 and 5 shed light on the fact that with too small quantity of base no reaction occurs. It can be explained by traces of acid such as acetic acid from the acetonitrile partitioning or the ammonium chloride quench of the reaction. Entry 2 seems to be the minima to deal with acid traces and perform the reaction, but it's slightly messier than entry 1.

The reaction time can be modified by the dilution factor, so the next parameter to be investigated was the concentration of the mixture (Scheme 31) and (Table 8).



Scheme 31: Dilution factor

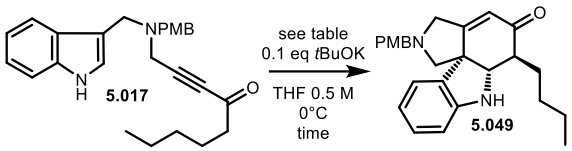
Entry	[C]	5.049 (%)	Comments
1	0.05 M THF	50-55	More degradations
2	0.1 M THF	65	Standard
3	0.2 M THF	69	Totally unexpected behaviour
4	0.3 M THF	73	
5	0.4 M THF	79	
6	0.5 M THF	85	
7	0.7 M THF	74	Slurry
8	0.5 M CH_3CN	80	
9	0.5 M Toluene	30	30 % of **5.019** and 30 % of **5.020**
10	0.5 M THF + 1 eq. H_2O	/	Full degradations

Table 8: Analysis of concentration factor

The outcome of the dilution table was surprising. The yield increased with the concentration of the reaction with a maximum of 85 % at 0.5 M. With higher concentration (entry 7) the mixture behaves as a slurry and the base was most likely not able to dissolve properly anymore. Entry 8, the reaction in acetonitrile at 0.5 M was successful. As a reminder, in toluene at 0.1 M the reaction provided only **5.020**. Interestingly, in entry 9, with toluene at 0.5 M we obtain a mixture of all three products **5.049**, **5.019** and **5.020**. This is a total modification of the mechanism as 60 % of the reprotonation

occurs from the other face by just increasing the concentration. Entry 10 furnishes again the fact that Gassman base[6] is improper for this reaction.

The last studied factor was time as the concentration was increased, it should be reduced (Scheme 32) and (Table 9).



Scheme 32: Reaction time investigation

Entry	Time (s)	Outcome
1	300	Finished (no starting material or intermediates detected)
2	120	
3	60	
4	30	
5	15	

Table 9: Consideration of reaction time

The reaction is finished even after 15 seconds, which correspond to the time *t*BuOK takes to dissolve. Then the product starts to decompose.

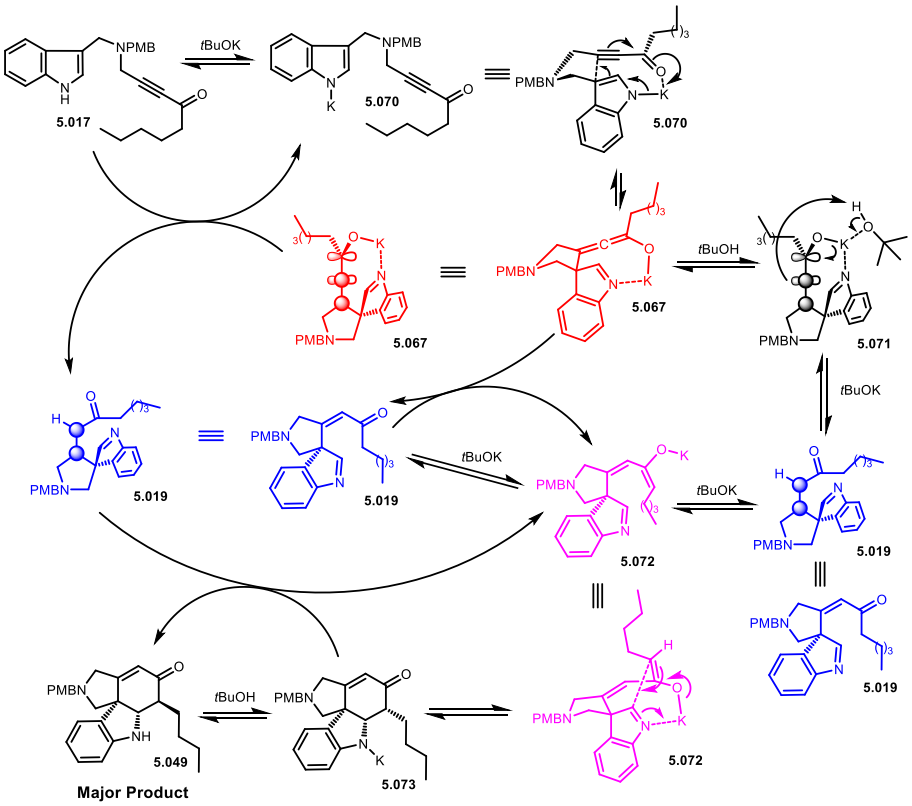
[6] Gassman, P. G.; Hodwon, P. K. G.; Balchunis, R. J. *J. Am. Chem. Soc.* **1976**, *98*, 1275.

8. Final mechanism

The final mechanism proposed for this reaction is based on all the data collected so far. Some details make us consider the fact that every deprotonation-reprotonation process should be between different stages of our products, not with *t*BuOK/*t*BuOH. A reaction so fast and which need such a high concentration is probably not using an intermediate molecule such *t*BuOH. And *t*BuOK is needed as activator, therefore the following mechanism is based on plausible deprotonation-reprotonation between intermediates. **BUT** we suspected that *t*BuOK/*t*BuOH approach is still credible.

So, the final mechanism of TGAP in THF 0.5 M with *t*BuOK as base is a combination of both possibilities (Scheme 33).

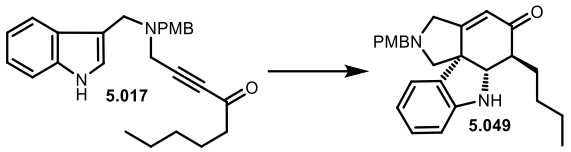
The first step is the metallation of starting material **5.017** into **5.057** by *t*BuOK. This potassium adduct **5.070** could undergo an intramolecular 5-*exo*-*dig* cyclization on the ynone moiety leading to chelate **5.067** (red). In the presence of *tert*-butanol, it will coordinate the potassium and perform an external facial reprotonation (as internal looks forbidden in dry THF) into the first observed intermediate **5.019** (blue). In the absence of *tert*-butanol, the allenolate **5.067** (red) is basic enough to deprotonate indole **5.017**, allenolate **5.067** (red) becomes intermediate **5.019** (blue) and indole **5.017** starts the cyclization as **5.070**. Intermediate **5.019** (blue) can be deprotonated by *t*BuOK or by allenolate **5.067** (red) into enolate **5.059** (pink). As we explained earlier, *E*-enolate is more favoured in this system and furnishes **5.073** by an intramolecular 6-*exo*-*trig* cyclization. Potassium indoline **5.073** is probably the stronger base of this reaction and should be able to metallate any other "acidic adduct" such as indole **5.017**, intermediate **5.019** (blue) or *tert*-butanol turning itself into the final product **5.049** (Scheme 33).



Scheme 33: Final mechanism

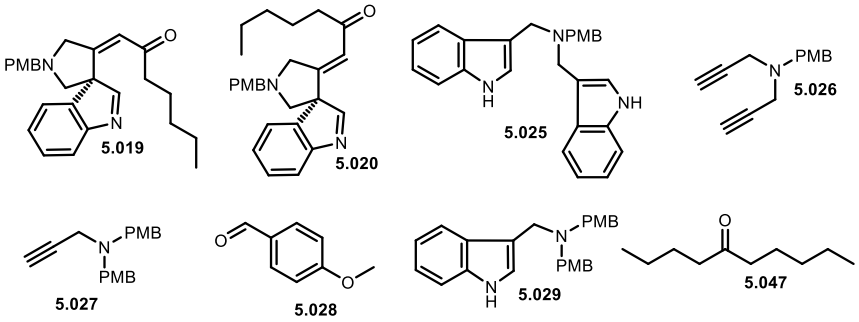
9. Conclusions

We discovered a new type a polycyclization based on the intramolecular cyclization of indole on ynone, to afford the tetracycle **5.049** (Scheme 34).



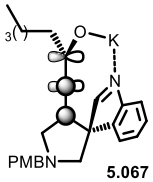
Scheme 34: New polycyclization

Different intermediates and side products were isolated such as **5.019**, **5.020**, **5.025**, **5.026**, **5.027**, **5.028**, **5.029 and 5.047** (Scheme 35).



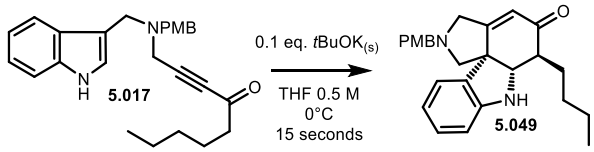
Scheme 35: Intermediates and side products

During optimisation process we proved that *t*BuOK was probably the best base for this reaction. As potassium can coordinate the indolenine moiety simultaneously with the allenolate **5.067** (Scheme 36).



Scheme 36: Potential indolenine-allenolate

Optimal conditions were unexpected because this intramolecular polycyclization needed a high concentration to furnish the best yield (Scheme 37).

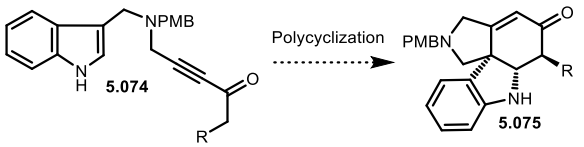


Scheme 37: Final conditions of TGAP

Finally, several mechanisms were proposed to explain the empirical data that we obtained (Scheme 7), (Scheme 10), (Scheme 14), (Scheme 20), (Scheme 21), (Scheme 22), (Scheme 24), (Scheme 29) and (Scheme 33).

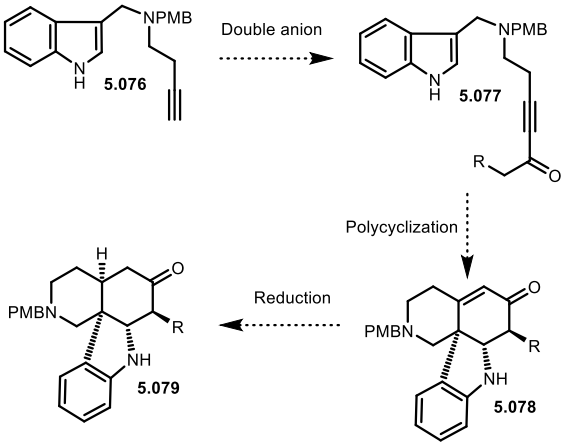
10. Perspectives

This polycyclization was tested with only one side chain so far. A simple way to extend the methodology would be the use of various side chains (noted R) in **5.074** to obtain a library of tetracyclic compounds **5.075** (Scheme 38).



Scheme 38: Extension of library

Application of the double anion chemistry on butyne **5.076** to obtain precursor **5.077** and finally application of our conditions toward tetracycle **5.078**. This tetracycle **5.078** is our main target because it could be reduced into the correct indole manzamine diastereoisomer **5.079** (Scheme 39).

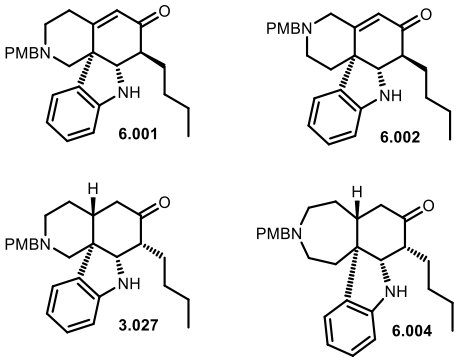


Scheme 39: Main target 5.079

Chapter VI

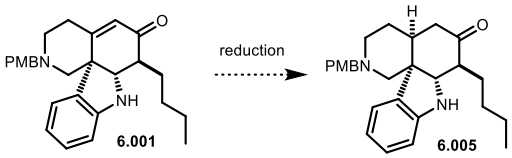
Application of the Polycyclization

This chapter will be devoted to the application and extension of our methodology towards the synthesis of various target molecules. The tetracycles **6.001** and **6.002** could be obtained directly with our ynone polycyclization methodology. The molecule **3.027** is a tetracycle produced through the second-generation methodology, a test with our condition could be interesting and finally the [7,6] tetracycle **6.004** could be as well a test of our conditions on a new compound based on SGAP (Scheme 1).



Scheme 1: Target tetracycles

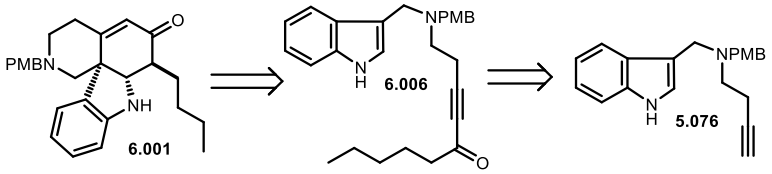
As a reminder the saturated tetracycle **6.005** resulting from the reduction of **6.001** is our target, as it possesses the desired stereocentres (Scheme 2).



Scheme 2: Desired stereorelationship

1. Synthesis of ynone 6.006

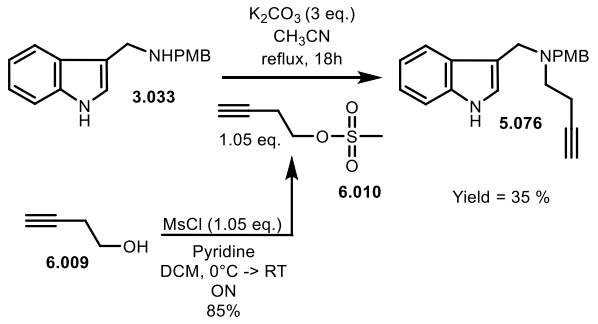
Tetracycle **6.001** should come from the polycyclization of ynone **6.006**, itself a product of the double anion chemistry applied to **5.076** reacted with a Weinreb amide as explained in the chapter V (Scheme 3).



Scheme 3: Retrosynthesis

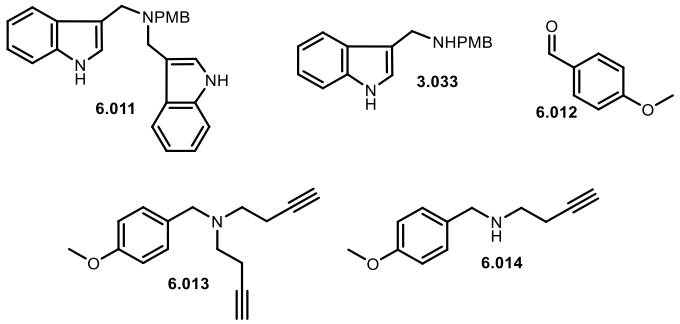
a. Alkylation

The butyn-amine **5.076** results from direct N-alkylation of the secondary amine **3.033** with mesylate **6.010**. The formation of the mesylate was performed from commercially available alcohol **6.009** in good yield (Scheme 4).



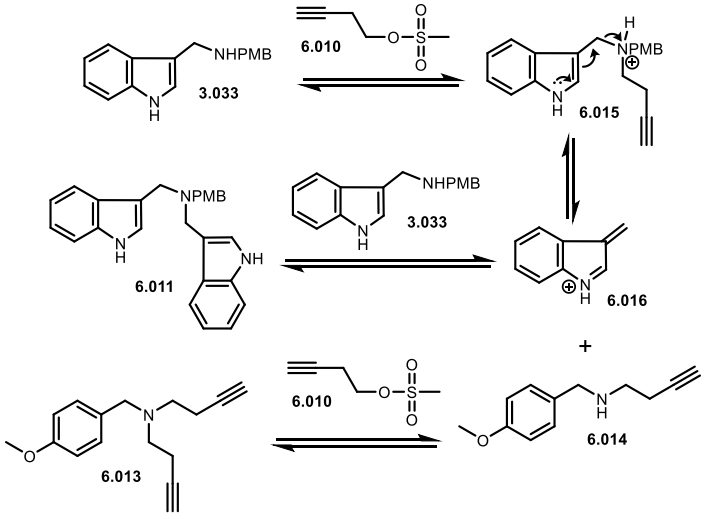
Scheme 4: Synthesis of tertiary amine 5.076

The alkylation itself was problematic as the yield did not get higher than 35 %. Several products were isolated and identified amongst them the bis-indole **6.011**, the starting material **3.033**, anisaldehyde **5.028**, tertiary amine **6.013** and secondary amine **6.014** (Scheme 5).



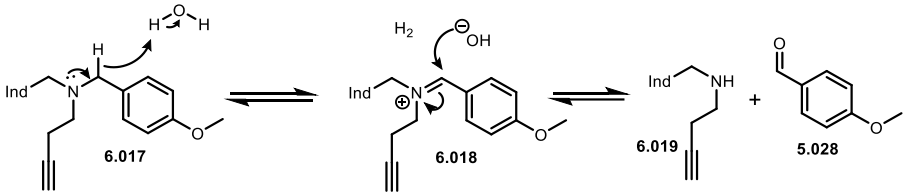
Scheme 5: Isolated side products

The presence of these undesired by-products is rationalized in the following lines. The main difference between the present alkylation and the propargylation in chapter V is an increase of the temperature. The ratio of side products has been modified, some of them were not even detected compared to the propargylation (*Cf.* Chapter V). The higher temperature of the reaction should increase the elimination rate of the ammonium **6.015** into ene-indoleninium **6.016** and the secondary amine **6.014**. As proposed earlier, **6.016** could then react with the starting material to furnish the bis-indole tertiary amine **6.011**. When the secondary amine **6.014** is N-alkylated a second time, and the undesired bis-alkylated amine **6.013** is formed (Scheme 6).



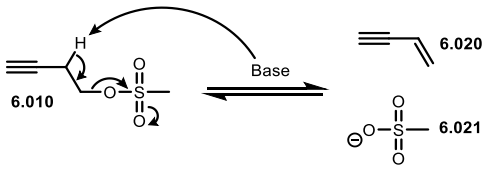
Scheme 6: Degradation mechanism

In chapter V, the presence of anisaldehyde **5.028** was explained by elimination or by a Cope-Like rearrangement. In this case, the Cope rearrangement cannot occur, so the formation of **5.028** is probably channelled throughout the elimination depicted in Scheme 7. The process starts with α-hydride elimination from substrate **6.017** to reduce water, then addition of hydroxide on the iminium **6.018** promotes the formation of an unstable hemiaminal that collapses into secondary amine **6.019** and anisaldehyde **5.028** (Scheme 7).



Scheme 7: Anisaldehyde 5.028 formation

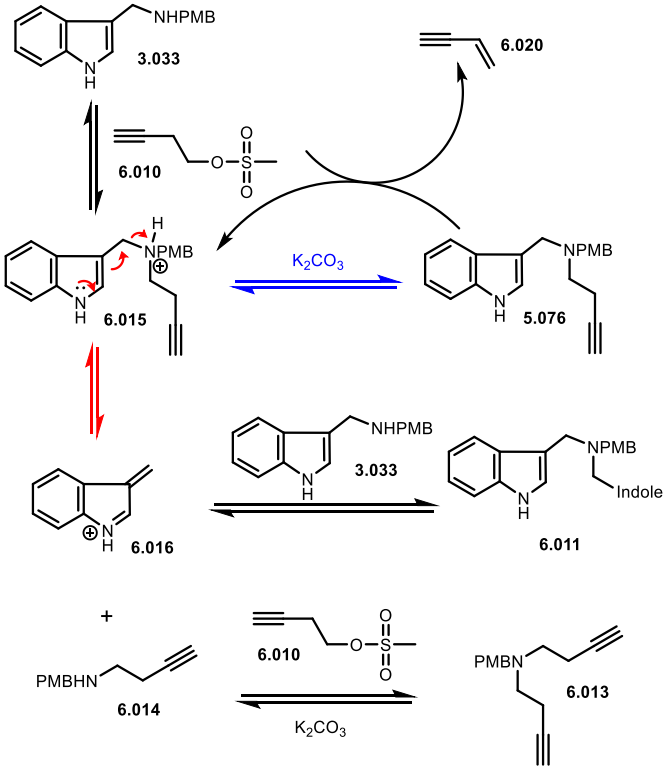
The presence of starting material **3.033** (25 %) in the final mixture was unexpected and surprising as no remaining mesylate **6.010** was found. In the mechanisms described *vide supra*, in each elementary step one equivalent of both is consumed to react or to fragment. The simplest conclusion is that mesylate **6.010** reacted to create something unobserved by NMR. Because of the acidity of the propargylic hydrogen in **6.010**, an acid-base reaction could potentially afford the stabilized and conjugated butenyne **6.020** and the mesylate anion **6.021** (Scheme 8).



Scheme 8: Elimination into 6.020

The base used in our conditions is potassium carbonate however, this alkoxide does not necessarily promote the elimination reaction. Most probably the secondary amine **3.033** or the desired product **5.076** could act as an intermediate base. The desired alkylated amine **5.076** is slightly more basic than the starting material **3.033**. So, the elimination (Scheme 9 in red)

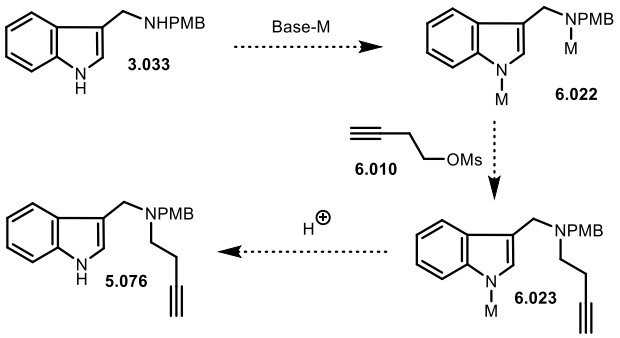
of the mesylate **6.010** into butenyne **6.020** could be catalyzed by the product. Unfortunately, this catalytic cycle is favoured because butenyne **6.020** possesses a boiling point of 5°C and the reaction occurs at reflux of acetonitrile. Our goal will be to find a way to favour the blue pathway without going back to the ammonium **6.015** (Scheme 9).



Scheme 9: Full degradation mechanism

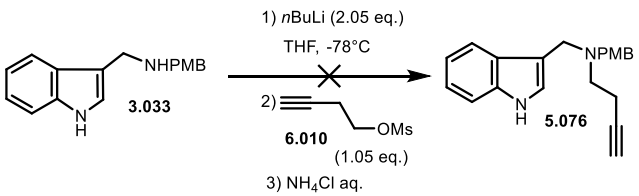
b. Double anion chemistry

One of the possibilities could be the use of anion. Double metallation of **3.033** into **6.022** could provide a better nucleophile, even at ambient temperature without the need for reflux. Therefore, this should avoid the ammonium **6.015**. Alkylation should be favoured for the amide and furnish the mono metallated intermediate **6.023**, which can be quenched by acidic media into our target molecule **5.076** (Scheme 10).



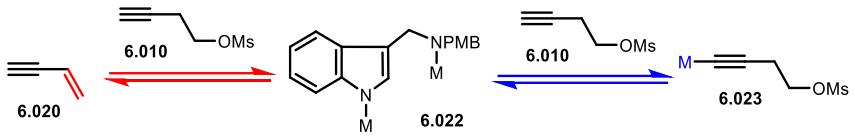
Scheme 10: Double anions mechanism

Unfortunately, with a base strong enough to deprotonate a secondary amine a new issue will be encountered, the acetylene deprotonation. Despite these bad offs, the test reaction was performed anyway. The metallation of the secondary amine **3.033** can be followed optically (the starting material is slightly yellow then slightly green with one equivalent of *n*BuLi then **6.022** is blood red at the end of addition). Addition of **6.010** creates an instantaneous change of colour towards yellow (Scheme 11).



Scheme 11: Double anions test

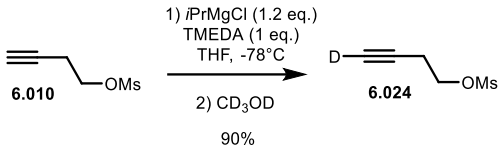
Finally, no alkylation product **5.076** was recovered, probably because of the suspected deprotonation of acetylene (in blue) and/or the elimination (in red) of the mesyl function into butenyne **6.020** (Scheme 12).



Scheme 12: Degradations of mesylate 6.010

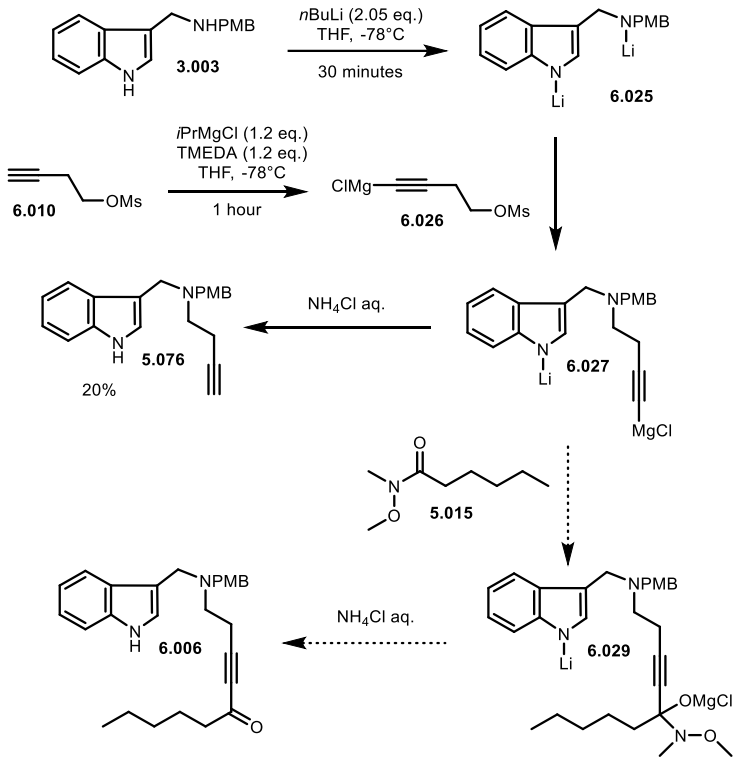
c. Triple anion chemistry

A solution to avoid the deprotonation of the terminus triple bond would be to voluntary deprotonate it. The use of isopropyl magnesium chloride and TMEDA afford the best results for the deuteration of **6.010** (Scheme 13)**.**



Scheme 13: Triple anions

Based on these observations we deprotonated the mesylate **6.010** prior to cannulation onto the bis metallated amine **6.025**. Unfortunately, 20 % was the best yield so far, because it is possible that lithium amide **6.025** prefers to act as a base instead of a nucleophile with **6.026** (Scheme 14).

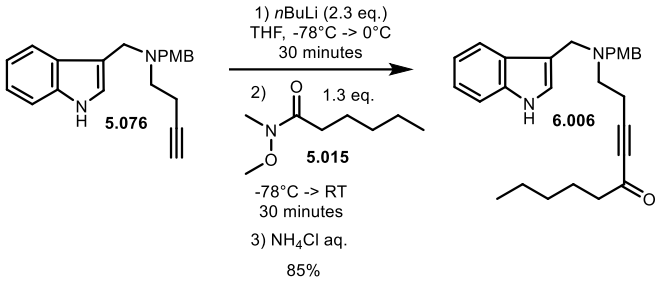


Scheme 14: Triple anions procedure

Of course, we could envision the use of bis anion **6.027** to directly react with our Weinreb amide **5.015** to obtain the precursor of polycyclization **6.006**. Many trans-metallations could be envisioned for this kind of chemistry, such as with zinc or copper. Both of them could provide a less basic and a more nucleophilic species from **6.025**. However, it is unclear if the trans-metallation of Grignard **6.026** to one of these metal centres could be prevented. However, those tests would be time consuming, so we decided to continue the synthesis with those poor yields.

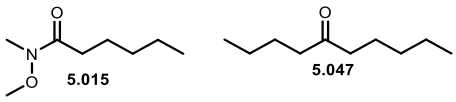
d. Synthesis of target ynone

Double metallation of butyne **5.076** with *n*BuLi and addition of Weinreb amide **5.015** occurred in a very good 85 % yield to give ynone **6.006** (Scheme 15).



Scheme 15: Ynone 6.006 synthesis

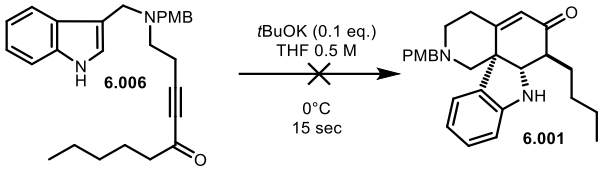
Besides the desired product **6.006**, some amounts of Weinreb amide **5.015** were recovered, along with decanone **5.047** derived from butyl addition onto the Weinreb amide. Partition between acetonitrile and hexane is able to remove most of it to access ynone **6.006** with high purity (Scheme 16).



Scheme 16: Observed side products

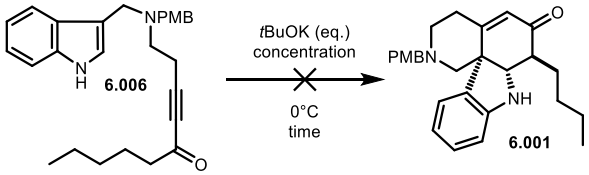
e. Polycyclization tests

The precursor **6.006** was exposed to the previously developed polycyclization conditions in hope to obtain the target molecule **6.001**. Unfortunately, only starting material **6.006** was recovered (Scheme 17).



Scheme 17: Polycyclization test

Several speculations were made, first the presence of acid traces (NH_4Cl from quench, acetic acid from acetonitrile, …) quenched the base. Secondly, maybe longer time is needed compared to the previous precursors. Third, dilution could be a problem as the precursors are different. Some tests should be performed (Scheme 18).

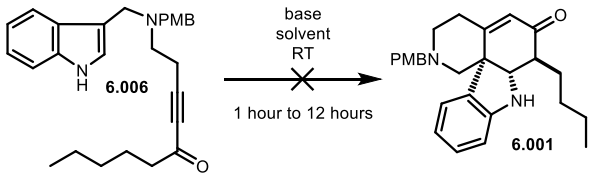


Tested conditions: A = 0.2 eq. *t*BuOK, 0.5M, 15 seconds;
B = 0.2 eq. *t*BuOK, 0.4M, 30 seconds; C = 0.2 eq. *t*BuOK, 0.3M, 30 seconds;
D = 0.2 eq. *t*BuOK, 0.2M, 60 seconds; E = 0.15 eq. *t*BuOK, 0.1M, 300 seconds;
F = 0.1 eq. *t*BuOK, 0.1M, 300 seconds; G = 0.2 eq. *t*BuOK, 0.1M, 300 seconds

Scheme 18: Polycyclization tests

Unfortunately, no conditions using more potassium *tert*-butoxide or a variation of concentration could afford product **6.001**. Entry **F** is an additional evidence of the presence of acidic hydrogen in the mixture because 0.1 eq. of base provides starting material **6.006** recovery when 0.15 or 0.2 creates decomposition. If the acid is NH_4Cl as suspected, simple calculation of the molar mass furnished that 1 % of the total weight would be enough to destroy 0.1 eq. of potassium *tert*-butoxide. The fact that decomposition can occur at every concentration is an unfortunate news.

As potassium *tert*-butoxide is not suitable for this cyclization, various alternative bases were tested to cyclize **6.006** into **6.001** (Scheme 19).

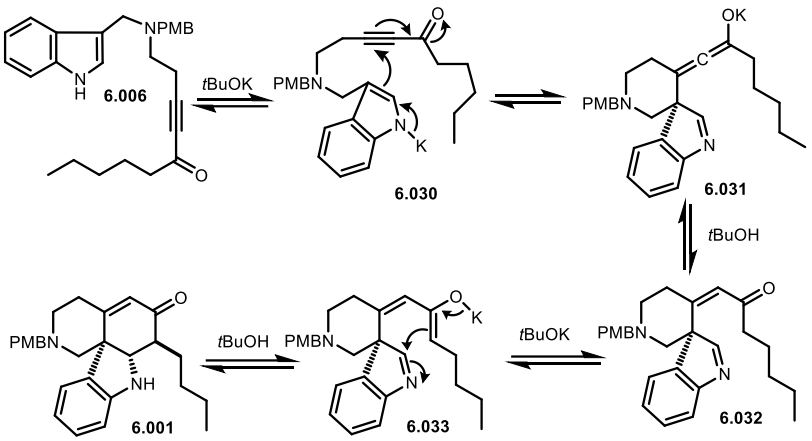


Tested conditions: A = 0.2 eq. DBU, THF; B = 0.2 eq. DBU, CH_3CN;
C = 0.2 eq. DBU, Toluene; D = 0.2 eq. TMG, THF; E = 0.2 eq. TMG, CH_3CN;
F = 0.2 eq. TMG, Toluene; G = 0.2 eq. *t*BuOLi, THF; H = 0.2 eq. *t*BuOLi, Toluene;
I = 0.2 eq. *t*BuONa, THF; J = 0.2 eq. *t*BuONa, Toluene.

Scheme 19: Polycyclization tests

DBU and TMG were successful in chapter V but, unfortunately, none of the tested conditions furnished more than decomposition (Entries A, B, C, D, E, F). Lithium and sodium *tert*-butoxide could have been suitable substitute for potassium, however, no product **6.001** was detected (Entries G, H, I, J). The decomposition rate was higher for DBU and TMG in acetonitrile and for *t*BuOLi and *t*BuONa in tetrahydrofuran (entries B, D, G, I).

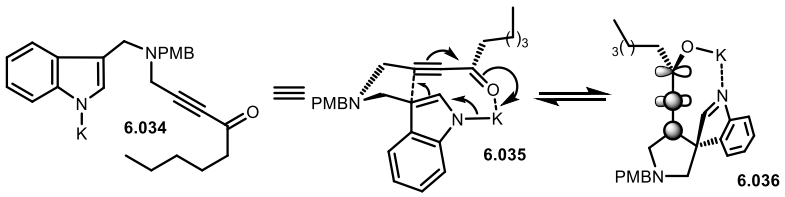
For an unexpected reason, the polycyclization does not occur at all here. To understand what the problem is we should take a closer look at the expected mechanism. Metallation of indole with the use of potassium *tert*-butoxide turns **6.006** into **6.030**. A 6-*exo*-*dig* cyclization **6.030** should occurs between the indole anion and the ynone moiety, this is allowed according to the Baldwin rules. This soft-soft addition forges **6.031**, as a base it can be reprotonated by any acid in the media, probably *tert*-butanol in our case to give enone **6.032**. This enone **6.032** can be deprotonated by potassium *tert*-butoxide to afford the enolate **6.033** which can cyclize in a 6-*exo*-*trig* fashion and deprotonate *tert*-butanol to furnish the desired product **6.001** (Scheme 20).



Scheme 20: Proposed mechanism for 6.001 cyclizations

Everything starting from intermediate **6.031** to the desired molecule **6.001** is similar to the precursor in the chapter V. But the final outcome is totally different as in our actual case, no product **6.001** and no first-cyclization product **6.032** could be observed. Those indications generate several hypotheses: the first would be some coordination problems with the metal. The second would be the transition state energy being probably too high. And finally, the third would be a substrate dependent issue.

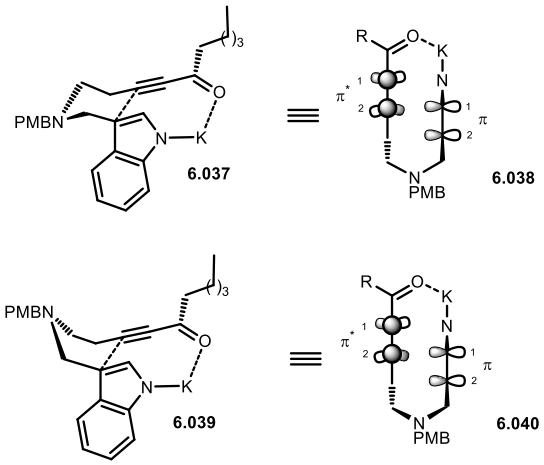
Hypotheses 1 and 2 come along, coordination between ynone and the metal was proposed in the chapter V. It's a possibility for the activation of ynone **6.034** and should increase the stability of the transition state **6.035** (Scheme 21).



Scheme 21: Mechanism of previous polycyclization

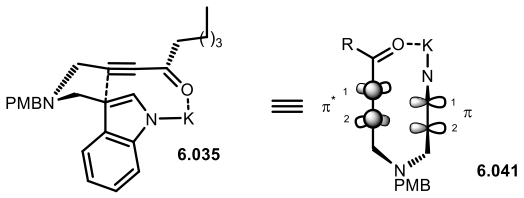
There are two classical transition states for this kind of system; chair **6.037** and boat **6.039**. With a chelation to potassium and from a top view

6.038 and **6.040**. In both cases overlap between the π orbital of indole and the π* orbital of the triple bond is needed. But as the sticks model show here, the overlap between the reactive positions π2 and π*2 looks really weak. Of course, this is a major issue for the reactivity and could explain why no product could be observed (Scheme 22).



Scheme 22: Expected transition states

The same top view projection **6.041** was made from the previous precursor **6.035**. The overlap between the reactive positions π2 and π*2 looks efficient enough for a reaction (Scheme 23).

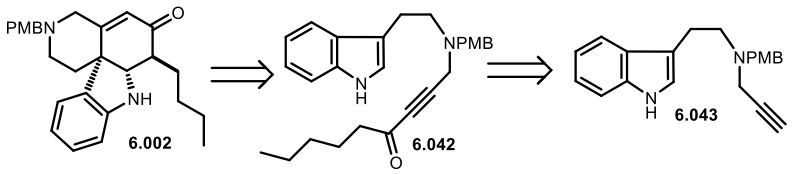


Scheme 23: Third expected transition state

The third hypothesis was the fact that this issue is only related to ynone **6.006** for unknown reason. If it really is a problem of the transition state in the 6-membered ring as we suspect, the easiest solution would be to make a same size ring analogue of the precursor **6.006** and see if it is able to cyclize.

2. Synthesis of tryptamine tetracycle

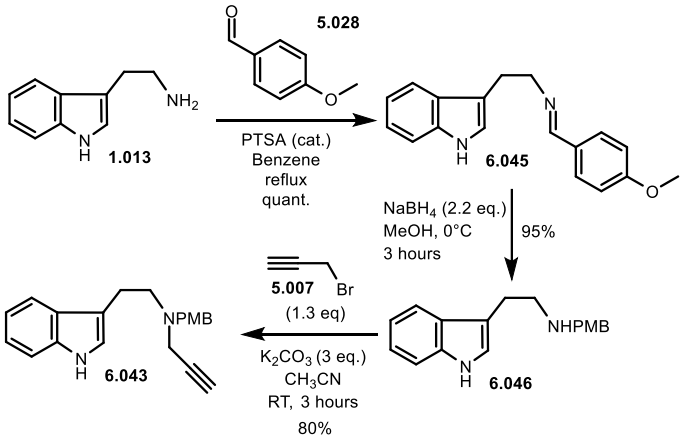
In order to find out more about the lacking reactivity, we planned to synthesize ynone **6.042**. If the polycyclization is successful, it provides the tetracycle **6.002** which is a closely related isomer of our target molecule **6.001**. Ynone **6.042** could be synthetized from propargyl **6.043** (Scheme 24).



Scheme 24: Tryptamine derivative retrosynthesis

a. Synthesis of tryptamine ynone

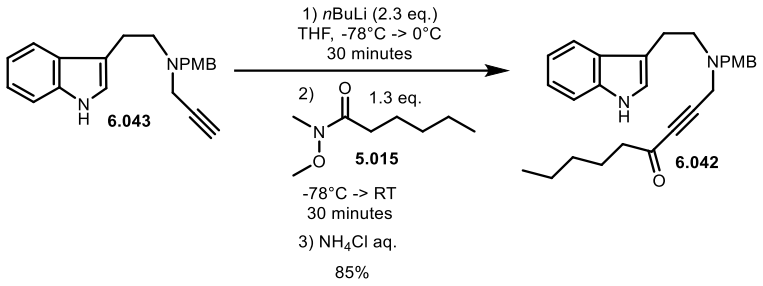
Tryptamine **1.013** and anisaldehyde **5.028** were condensed into imine **6.045** and directly reduced into the secondary amine **6.046**. The amine was alkylated with propargyl bromide **5.007** to furnish tertiary amine **6.043** in a very good overall yield of 75 % over three steps (Scheme 25).



Scheme 25: Tryptamine 6.043 synthesis

The double anion methodology combined to the addition of Weinreb amide **5.015** was successful for the third time. The conversion of **6.043** into

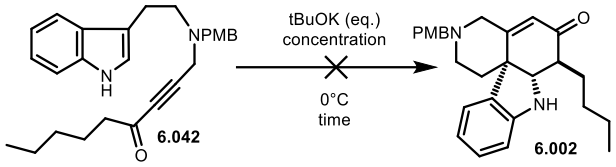
ynone **6.042** was achieved with a yield of 85 % and the purification was aided by portioning between acetonitrile and *n*-hexane (Scheme 26).



Scheme 26: Third ynone synthesis

b. Polycyclization tests

With a third ynone in hands, the polycyclization tests were started (Scheme 27).

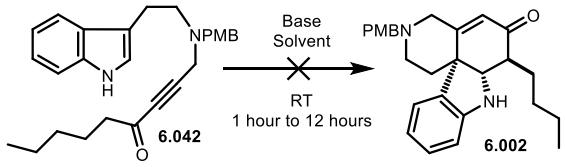


Tested conditions: A = 0.2 eq. *t*BuOK, 0.5M, 15 seconds;
B = 0.2 eq. *t*BuOK, 0.4M, 30 seconds; C = 0.2 eq. *t*BuOK, 0.3M, 30 seconds;
D = 0.2 eq. *t*BuOK, 0.2M, 60 seconds; E = 0.2 eq. *t*BuOK, 0.1M, 300 seconds.

Scheme 27: Polycyclization tests

To our greatest disappointment, the attempts with potassium *tert*-butoxide met with failure. No reaction was observed at different concentrations and reaction times, and in each case only decomposition was observed (Entries A, B, C, D and E).

In order to investigate if a more suitable base can be found, some other bases were screened (Scheme 28).



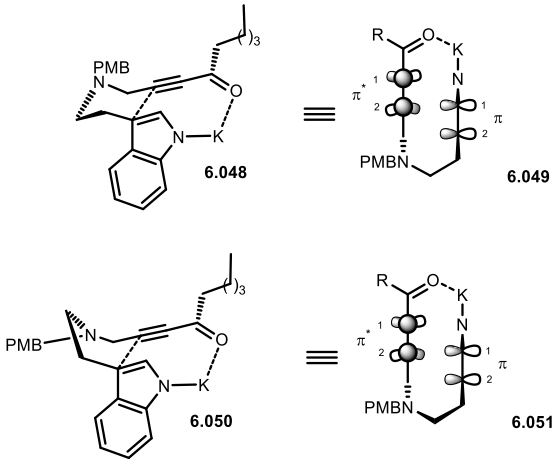
Tested conditions: A = 0.2 eq. DBU, THF; B = 0.2 eq. DBU, CH_3CN;
C = 0.2 eq. DBU, Toluene; D = 0.2 eq. TMG, THF; E = 0.2 eq. TMG, CH_3CN;
F = 0.2 eq. TMG, Toluene; G = 0.2 eq. *t*BuOLi, THF; H = 0.2 eq. *t*BuOLi, Toluene;
I = 0.2 eq. *t*BuONa, THF; J = 0.2 eq. *t*BuONa, Toluene.

Scheme 28: Polycyclization tests

As for the precursor **6.006**, none of those bases provided the target molecule. Decomposition in acetonitrile appears faster than in THF and toluene (Entries B, F). Finally, similar to potassium *tert*-butoxide, sodium and lithium analogues of the base also furnished also decomposition (Entries G, H, I, J).

c. Speculated transition states

The same type of transition states can be proposed; chair **6.048** or boat **6.050**. Again, the overlap between the reactive positions π2 and π*2 looks weak (Scheme 29).



Scheme 29: Plausible transition states

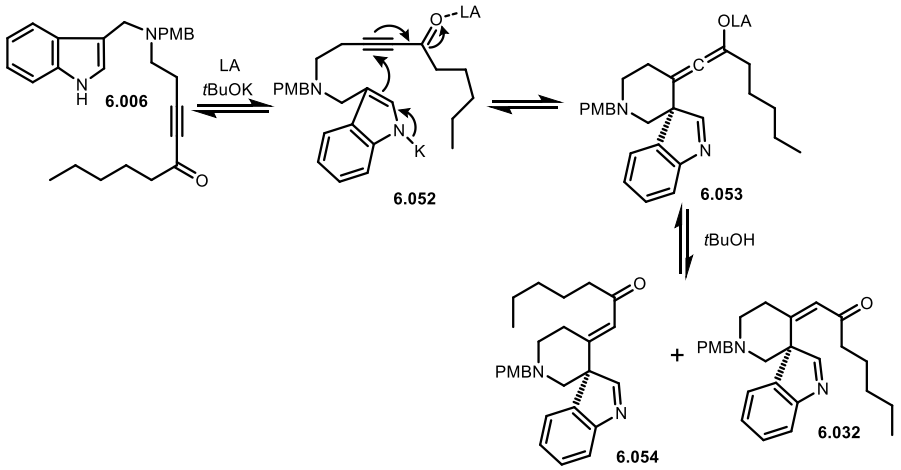
This statement revokes the third hypothesis (*Cf.* Chapter VI), according to which the cyclization problem was substrate dependant.

A proper way to polycyclize those two precursors **6.006** and **6.042** is needed. Potassium *tert*-butoxide was acting as base and potential Lewis acid. The use of base and Lewis acid at the same time could maybe solve this issue.

3. Polycyclization tests with Lewis acid and bases

a. Potential issue

As explained in the chapter V, there are two possibilities for the reprotonation of the intermediate. The use of Lewis acid was obvious, but it can totally modify the reprotonation mechanism. Activation of ynone by Lewis acid and metallation of indole by potassium *tert*-butoxide provides **6.052** which can cyclize into **6.053**. The stability of intermediate **6.053** will be adapted to the Lewis acid but unfortunately without the speculated cyclic form, the reprotonation could happen from both faces, and a higher proportion of undesired **6.054** could be observed this time (Scheme 30).

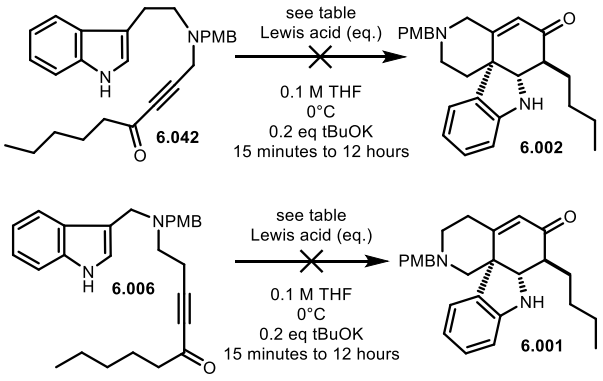


Scheme 30: Postulated mechanism for co-catalysis

b. *t*BuOK + Lewis acid

Potassium *tert*-butoxide is probably not the best choice as Lewis acid co-catalyst. Lewis acids often contain traces of Brønsted acid and *t*BuOK likes to perform metal exchange reactions.

Both precursors **6.042** and **6.006** were tested with various Lewis acids (Scheme 31).



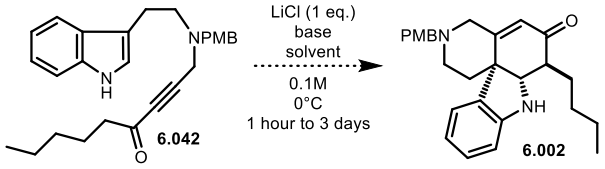
Tested conditions: A = 1 eq. LiCl; B = 0.15 eq. CuCl; C = 1 eq. $ZnCl_2$; D = 1 eq. $Mg(OTf)_2$; E = 1 eq. $Zn(OTf)_2$; F = 0.2 eq. $Cu(OTf)_2$.

Scheme 31: Co-catalysed Polycyclization

Some of them are hard to activate the ketone and copper was used to activate the triple bond. The only outcome was starting material recovery, as suspected 0.2 eq. of potassium *tert*-butoxide was not the best choice. Since there was no modification with time, we suspect that our base was destroyed by acid traces or deactivated by coordination. However, an interesting information came out, no major decomposition was observed.

c. Strong organic bases + Lewis acid

DBU and TMG should be a potential solution to this situation and both bases were tested in a short screen (Scheme 32).



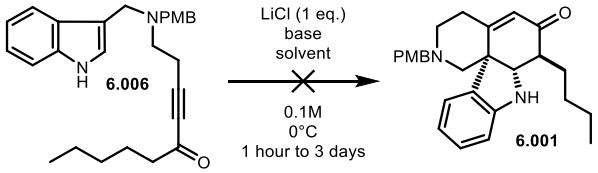
Tested conditions: A = 0.3 eq. DBU, CH_3CN; B= 0.7 eq. DBU, CH_3CN;
C = 1.2 eq. DBU, CH_3CN; **D**= 0.3 eq. TMG, CH_3CN; **E** = 0.7 eq. TMG, CH_3CN;
F = 1.2 eq. TMG, CH_3CN; **G** = 0.3 eq. DBU, THF; **H** = 1 eq. DBU, THF;
I = 0.3 eq. TMG, THF; **J** = 1 eq. TMG, THF.

Scheme 32: Lithium chloride co-catalysed polycyclization

Lithium chloride as co-catalyst with DBU in acetonitrile proved successful in the literature.[1] However, these conditions appeared to be unsuccessful with our tryptamine starting material **6.042**. In entries A, B, D, E, G, H, I and J where the quantity of base was lower or equal to the quantity of Lewis acid, no reaction occurred, not even decomposition. This observation tends to correlate with the absence of free base in the mixture. A slow decomposition could be observed when the quantity of base is higher than the quantity of Lewis acid (Entries C and F). So far, no cyclized product could be observed with the use of Lewis acid.

[1] Kanematsu, M.; Yoshida, M.; Shishido, K. *Angew. Chem.* **2011**, *123*, 2666.

The same conditions were tested on the substrate **6.006** (Scheme 33).



Tested conditions: A = 0.3 eq. DBU, CH_3CN; B= 0.7 eq. DBU, CH_3CN;
C = 1.2 eq. DBU, CH_3CN; **D**= 0.3 eq. TMG, CH_3CN;
E = 0.7 eq. TMG, CH_3CN; **F** = 1.2 eq. TMG, CH_3CN; **G** = 0.3 eq. DBU, THF;
H = 1 eq. DBU, THF; **I** = 0.3 eq. TMG, THF; **J** = 1 eq. TMG, THF.

Scheme 33: Lithium chloride co-catalysed polycyclization

Unfortunately, the exact same outcome was observed with this precursor **6.006**. A slight excess of bases favoured decomposition (entries C and F). No reaction was observed in the case where the amount of lithium chloride was equal or superior to the amount of base. The decomposition of starting material with DBU is almost complete in 3 hours without lithium chloride. The decomposition observed in entries C and F is slower with LiCl. The use of Lewis acid does not promote the cyclization of our product **6.006**. However, lithium chloride can “protect” our product from decomposition, most probably by coordination with the nitrogenated-base.

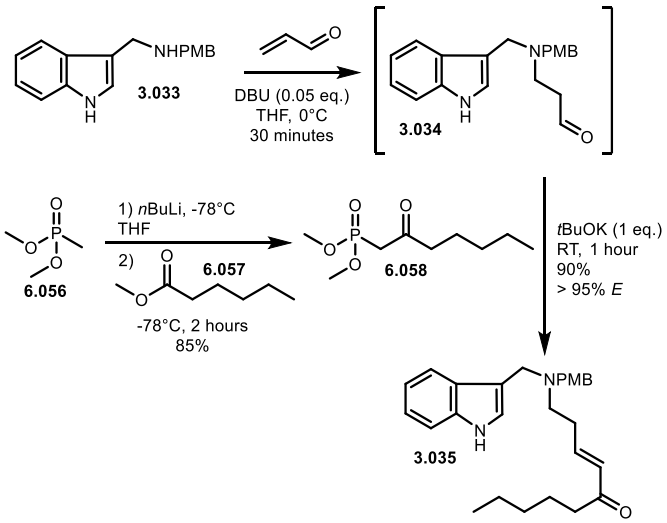
Many different Lewis acids could be envisioned to favour this cyclization, but most of them will be coordinated by the base and probably quench the reaction. At this point, no co-catalytic system using base and Lewis acid could provide the desired tetracycles **6.001** and **6.002**.

4. Application of our methodology to enone of SGAP

A test of our polycyclization conditions must be made on the enone precursor of the second generation.

a. Synthesis of enone

The procedure developed by Laurent Turet[2] was followed to obtain the enone **3.035**, starting from amine **3.033**, acrolein and β-keto phosphonate **6.058**. Phosphonate **6.056** was stirred with *n*BuLi at -78°C then methyl hexanoate **6.057** was added to obtain β-keto phosphonate **6.058**. Amine **3.033** was then alkylated using acrolein and a catalytic amount of DBU. Then, aldehyde **3.034** underwent a Horner-Emmons reaction with the potassium anion of β-keto phosphonate **6.058**. The enone **3.035** was obtained in a very good yield and with a high *E* selectivity >95 % (Scheme 34).

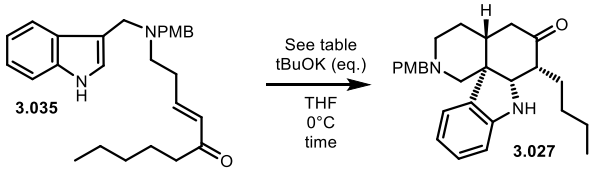


Scheme 34: Synthesis of enone 3.035

[2] Turet, L. *PhD Thesis* **2004**, Université catholique de Louvain.

b. Tests TGAP with *t*BuOK on enone

The polycyclization conditions were tested on enone **3.035** in view of the tetracycle **3.027** (Scheme 35) and (Table 1).



Scheme 35: Polycyclization tests

Entry	*t*BuOK	[C]	Time	3.035	3.027
1	0.1 eq.	0.1	1h	Full recovery	/
2	0.2 eq.	0.1	45 min	/	70 %
3	0.2 eq.	0.5	1 min	50 %	20 %
4	0.2 eq.	0.5	5 min	/	60 %

Table 1: Polycyclization tests

In entry 1, 0.1 eq. of potassium *tert*-butoxide does not promote the cyclization of **3.035**. Entry 2 shows almost identical conditions of SGAP (1 hour instead of 45 minutes and 0°C instead of ambient temperature) and it's working well. Entries 3 and 4 are TGAP conditions and the cyclizations occur as expected. A small variation of the yield can be observed between 0.1 M and 0.5 M in favour for 0.1 M.

The NMR observations correlate with Laurent Turet's work. Mono-crystals were extremely easy to obtain either from hot methanol, or from isopropanol evaporation, from recrystallisation using ethyl acetate and methanol and finally, from recrystallisation using ethyl acetate and hexane. The solved crystal structure reveals a chair-boat conformation, a *trans*-fused-junction and the expected *cis*-correlation between the side chain and indoline. The PMB function is oriented equatorial and the side chain got a pseudo-equatorial orientation (Figure 1).

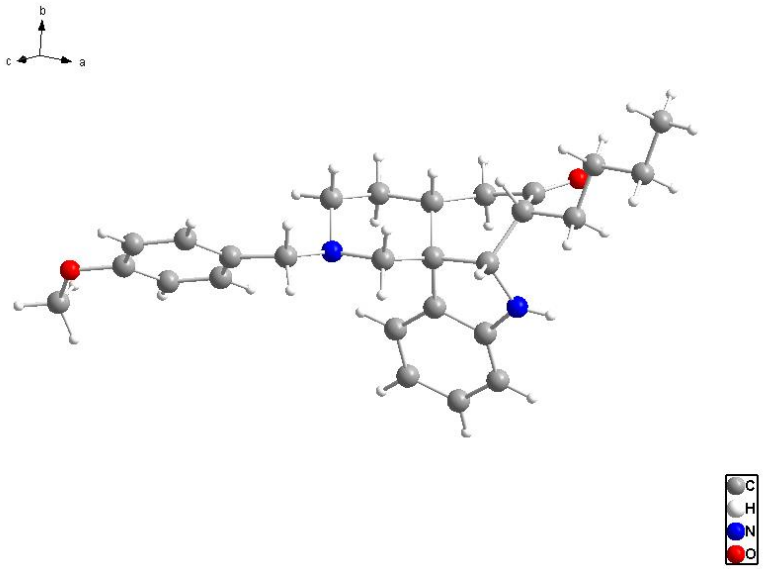
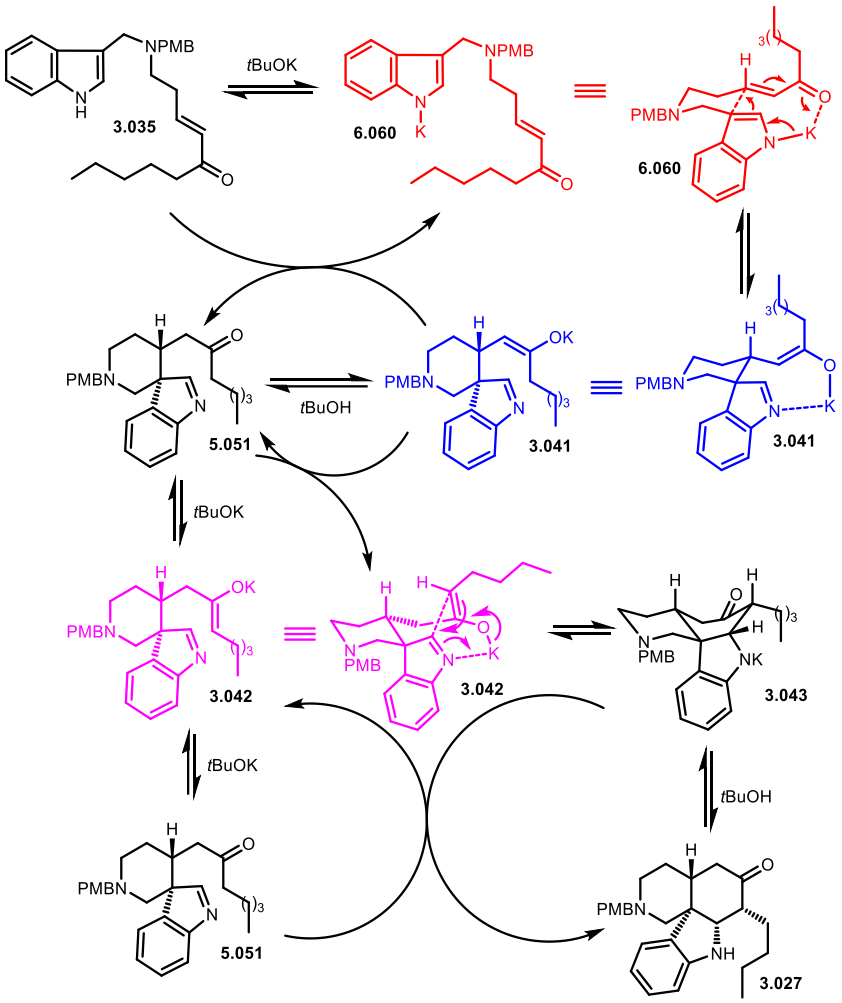


Figure 1: X-ray diffraction of 3.027

c. Final Mechanism proposal for enone

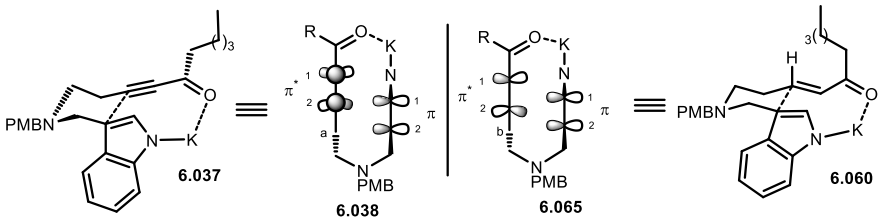
Since the cyclization is working in our conditions, we considered that the mechanism should be similar to the ynone cyclization involving potassium *tert*-butoxide as initiator to convert enone **3.035** to metallated indole **6.060** (red). This indole potassium could have chair-transition state with a coordination to the ketone. An eight electron Michael-addition could occur to afford enolate **3.041** (blue) which can equilibrate with *tert*-butanol to obtain ketone **5.051**. The same enolate **3.041** could do the activation of indole **3.035** as the pK_a difference is favourable. Ketone **5.051** could be deprotonated by potassium *tert*-butoxide or by enolate **3.041** to afford enolate **3.042** (pink). Potassium enolate **3.042** could then cyclize through a boat transition state into **3.043**. Finally, indoline potassium **3.043** could be reprotonated by *tert*-butanol or by a ketone like **5.051** into the desired product **3.027** (Scheme 36).



Scheme 36: Full mechanism for 3.027

The final part of this mechanism will be the analysis of the top projection of our proposed transition state. The main difference will come from the angle between the triple bond and carbon **a** and the double bond and carbon **b**. The 180° angle in **6.038** appears to make the triple bond to far from the indole to react properly. When the 120° in **6.065** slightly increases the vicinity between the two reactive parts. Both are working on a chair transition state and the second main difference is the size of the bond.

However, this parameter got a low impact since the bond itself is not located inside the chair transition state (Scheme 37).



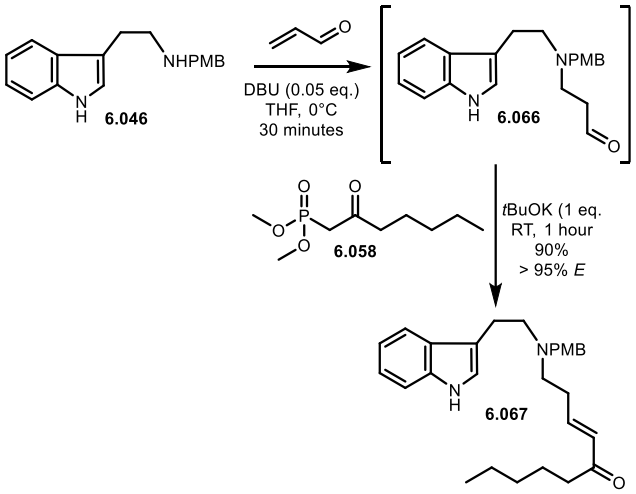
Scheme 37: Variation between 6.037 and 6.060

5. Application of the methodology to tryptamine enone 6.067

The same protocol could be used with tryptamine derivative **6.046** as starting material to synthetize a new enone **6.067**.

a. Synthesis of enone

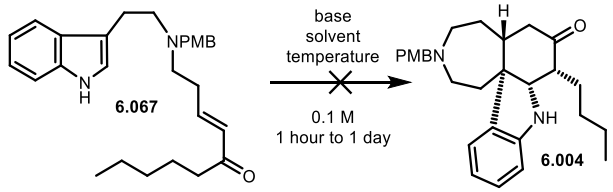
Amine **6.046** was stirred with acrolein and DBU to obtain aldehyde **6.066** that subsequently underwent an Horner-Emmons reaction with the potassium anion of β-keto-phosphonate **6.058**. *E*-enone **6.067** was obtained in very good yield with a high >95% selectivity (Scheme 38).



Scheme 38: Synthesis of enone 6.067

b. Tests TGAP with *t*BuOK on enone 6.067

Polycyclization attempts were made with this new enone to obtain the [7,6] tetracycle **6.004** (Scheme 39).



Tested conditions: **A** = 0.2 eq. *t*BuOK, THF, 0°C; **B** = 0.4 eq. *t*BuOK, THF, 0°C;
C = 0.2 eq. *t*BuOK, CH_3CN, 0°C; **D** = 0.3 eq. *t*BuOK, CH_3CN, 0°C;
E = 0.4 eq. DBU, THF, RT; **F** = 0.4 eq. DBU, CH_3CN, RT;
G = 1 eq. DBU + 1 eq. LiCl, CH_3CN, RT; **H** = 0.4 eq. TMG, THF, RT;
I = 0.4 eq. TMG, CH_3CN, RT; **J** = 1 eq. TMG + 1 eq. LiCl, CH_3CN, RT.

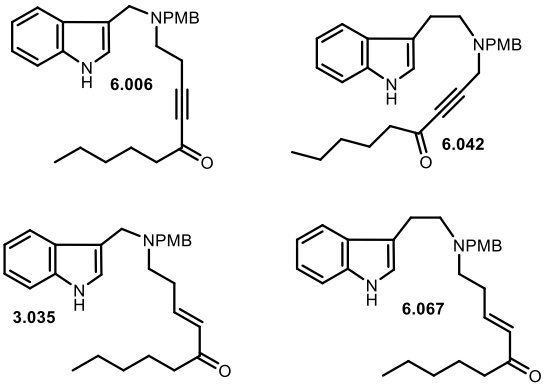
Scheme 39: Polycyclization of enone 6.067

Unfortunately, no cyclized products **6.004** could be observed or isolated. In entries A and C a small quantity of *t*BuOK did not provide anything expect starting material. When larger quantities were used, only decomposition was observed (entries B and D). DBU and TMG afforded a slow decomposition (entries E, F, H, I). However, the time needed to decompose all the starting material was tremendously longer than for ynones. Finally, the use of lithium chloride only furnished starting material (entries G and J).

There was a very high probability for this polycyclization to fail, according to our knowledge so far. The addition of one carbon to ynone lead to a major issue for the cyclization. The addition of one carbon to enone will very likely give the same kind of outcome.

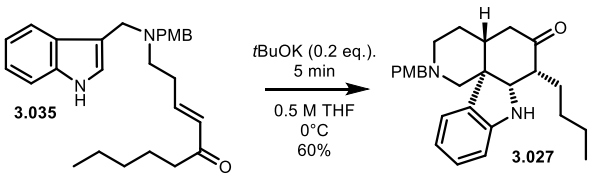
6. Conclusions

In an attempt to reach tetracycles, the four polycyclization precursors **6.006**, **6.042**, **3.035**, **6.067** were synthetized (Scheme 40).



Scheme 40: Ynones and enones synthetized

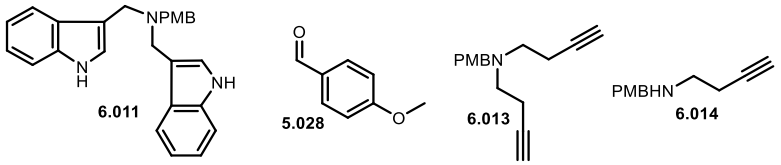
Among them only **3.035** was suitable for polycyclization into **3.027** (Scheme 41).



Scheme 41: Successful polycyclization

The structure and conformation of **3.027** was established by NMR and X-ray diffraction.

Various side products were isolated, such as bis-indole **6.011**, anisaldehyde **5.028**, tertiary amine **6.013** and secondary amine **6.014** (Scheme 42).

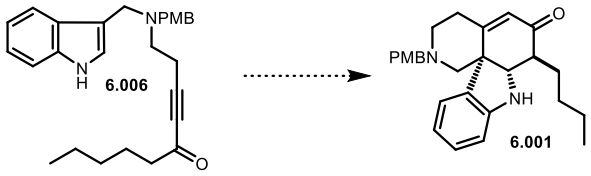


Scheme 42: Isolated side products

Mechanistical speculations were proposed to explain the lacking cyclization of **6.006**, **6.042** and **6.067** (Scheme 20, Scheme 21, Scheme 22, Scheme 23, Scheme 29, Scheme 30, Scheme 36, Scheme 37). And were probably due to high energy transition states or transition states' conformational issues.

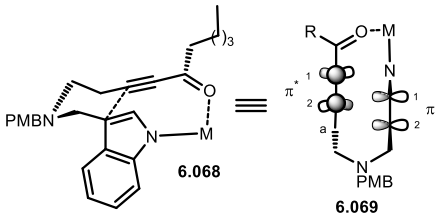
7. Perspectives

Lithium, sodium and potassium *tert*-butoxide were unsuccessful promoters for the polycyclization of **6.006**, **6.042** and **6.067** (Scheme 43).



Scheme 43: Expected polycyclization

According to actual knowledge, potassium prefers 3 or 4 coordinations including solvent with tetrahedral geometry. A variation in the metal for something with higher coordination abilities would change the angle OMN (ketone-metal-indole). This could allow a modification in the transition state and increase the vicinity of the reactive sites (Scheme 44).



Scheme 44: Mechanistical variation

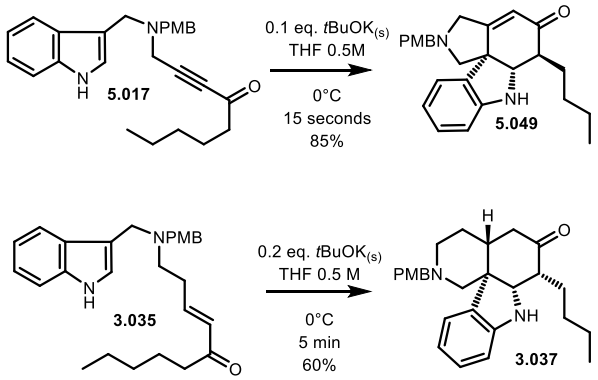
Almost all metals exist as a *tert*-butoxide salts, however, caesium, barium and cerium (III and IV) should be tested in priority as they possess a similar coordination number (up to 9), a similar atomic mass, and their *tert*-butoxide salts can still exhibit some basicity.

Chapter VII

Fourth Generation Anionic Polycyclization

1. Hypotheses

Several mechanistic proposals were suggested throughout the chapters V and VI. In chapter V, cyclization of ynone **5.017** into [5,6] tetracycle **5.049** furnished some insight into the mechanism. In chapter VI, cyclization of enone **3.035** into [6,6] tetracycle **3.037** shed even more light on the pathway. This chapter will be devoted to the development of a new type of polycyclization based on the successes and failures of the previous chapters (Scheme 1).

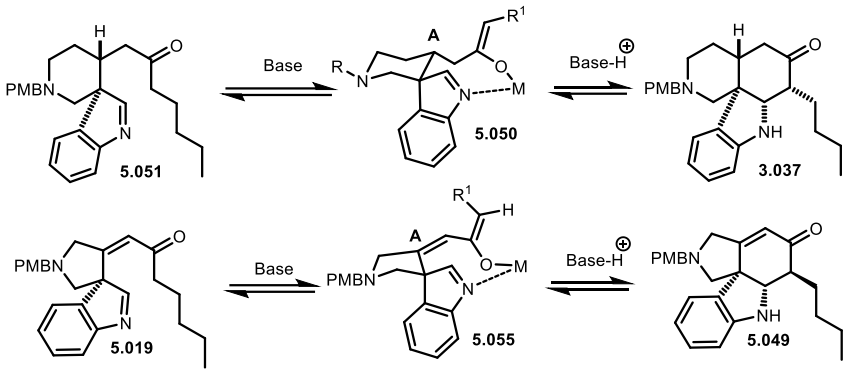


Scheme 1: Successful polycyclizations

a. Hypothesis 1: Side chain selectivity

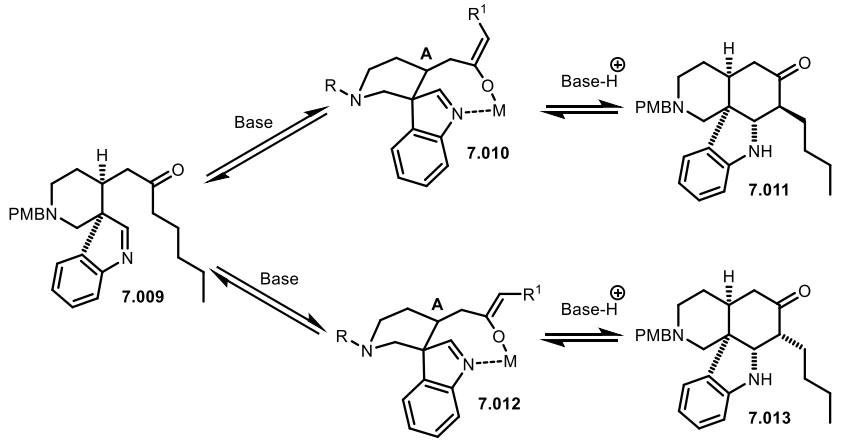
We speculated that the steric hindrance at carbon **A** possesses a prime impact on the side chain selectivity. The second cyclization of the enone precursor **5.051** gave **5.050** as potential intermediate. In the case of

the second cyclization of ynone **5.019**, the intermediate could be **5.055** (Scheme 2).



Scheme 2: Speculated intermediates

If this assumption is correct, there is reason to believe that the cyclization of a molecule like **7.009** would lead to **7.011**. On the other hand, transition state **7.012** appears sterically disfavoured due to interactions of the side chain R_1 and the metal centre (Scheme 3).

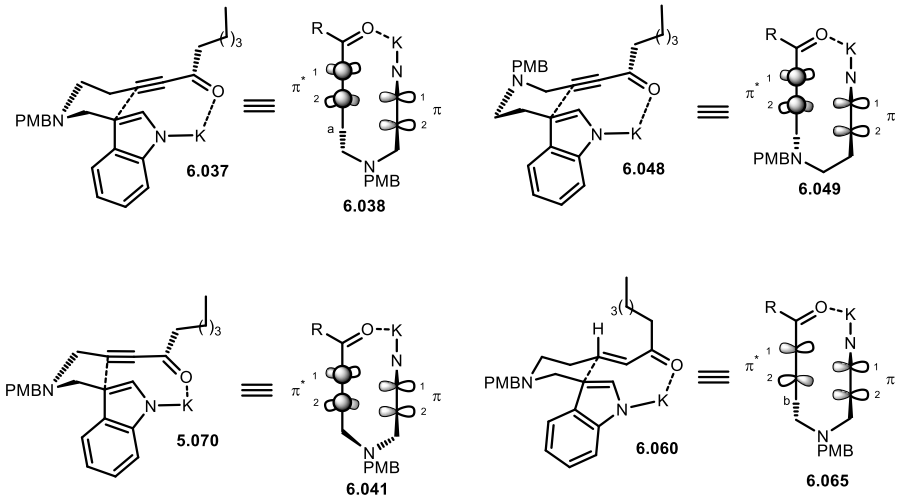


Scheme 3: Second cyclization of 7.009

Since **7.011** encompasses the desired relative configuration and according to our current knowledge, the synthesis of **7.009** should lead to tetracycle **7.011**.

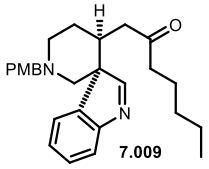
b. Hypothesis 2: size of the transition state

In chapter VI, an issue was encountered with the cyclization of ynones **6.037** and **6.048**. The weak overlap of the reactive orbitals is depicted respectively in structures **6.038** and **6.049** and was used to explain the lack in reactivity. Contrarywise, the cyclization of ynone **5.070** and enone **6.060** was successful and a good overlap was therefore speculated (Scheme 4).



Scheme 4: Overlap of orbital in the first cyclization

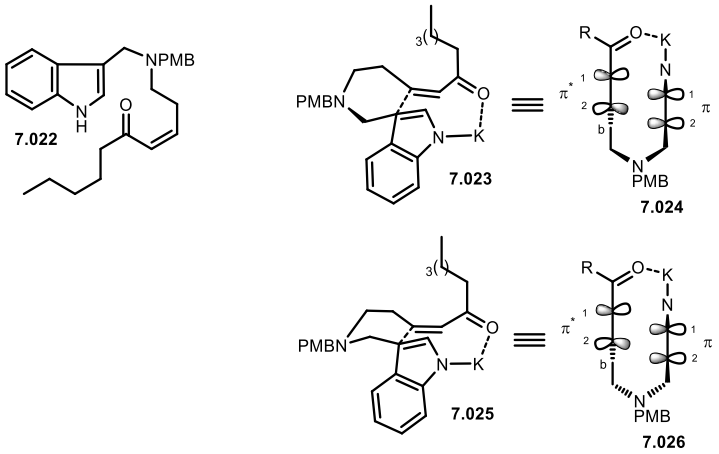
To synthesize the desired intermediate **7.009**, the estimation of the overlap should be done beforehand (Scheme 5).



Scheme 5: Target intermediate

c. Hypothesis 3: *Z*-enone?

The *Z*-enone **7.022** should embody the critical features. It is possible that the overlap in the *Z*-enone **7.022** and the corresponding *E*-enone **7.020** are very similar. The stick models of the chair conformer **7.023** and boat conformer **7.025** transition states look persuasive so far. The main issue in these transition states seems to be the steric hindrance generated by the protons of the double bond. This cyclization should furnish the desired intermediate **7.009** (Scheme 6).

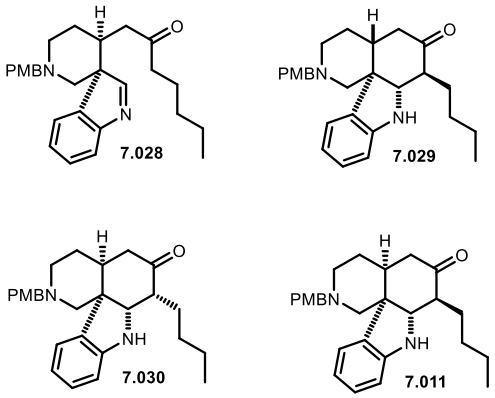


Scheme 6: *Z*-enone possibilities

According to our hypothesis, *Z*-enone **7.022** is very promising and a polycyclization should furnish the target molecule **7.011** with the desired stereo-relationships.

d. Confirmation or refutation

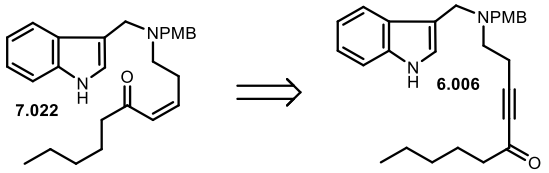
As a fourth type of substrate for polycyclization (*Cf.* chapter III and V), those tests will be called the fourth generation anionic polycyclization (FGAP). They will either strengthen or refute our previous statements and hypotheses. Four possible outcomes can be envisioned. In the event of no reaction or decomposition, hypotheses 2 and 3 will be disproven. The formation of **7.028**, **7.029**, and **7.030** will go in line with hypothesis 2 but disprove hypotheses 1 and 3. And finally, the formation of **7.011** will prove hypotheses 1, 2 and 3. No matter which tetracycle is obtained, all of them could have interesting bioactivities (Scheme 7).



Scheme 7: Possible outcomes

2. Lindlar reduction of ynones

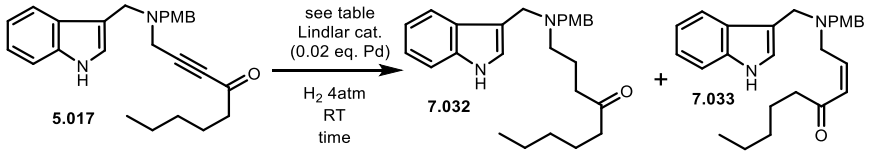
Potentially, the easiest way to synthesize *Z*-enone **7.022** would be through the Lindlar hydrogenation[1] of the previously reported ynone **6.006** (Scheme 8).



Scheme 8: Retrosynthesis of 7.022

a. Lindlar reduction of ynone 5.017

Test experiments were performed on **5.017**. Two major products could be expected, the unwanted saturated ketone **7.032** and the desired *Z*-enone **7.033** (Scheme 9) and (Table 1).



Scheme 9: Lindlar reduction of ynone 5.017

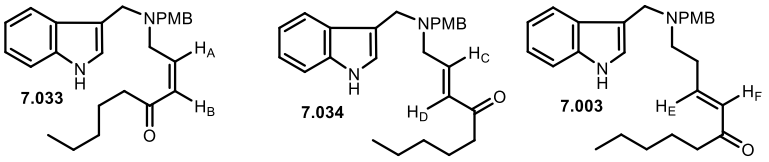
[1] Lindlar, H. *Helvetica Chimica Acta*. **1952**, *35*, 446.

Entry	Solvent	Quinoline (eq.)	Time	Ratio		
				5.017 (%)	7.032 (%)	7.033 (%)
1	EtOH	/	2h30	/	>95	/
2	EtOH	0.3	2h30	/	>95	/
3	EtOAc	/	2h30	/	30	70
4	EtOAc	0.3	2h30	/	50	50
5	Tol	/	15 min	75	/	25
6	Tol	/	1h	/	30	70
7	Benz.	0.5	1h	/	10	90

Table 1: Lindlar reduction of ynone 5.017

Lindlar reduction using ethanol with quinoline or without quinoline was in both cases too active and led only to the saturated product **7.032** (Entries 1 and 2). Aromatic solvents and ethyl acetate provide the *Z*-enone **7.033** (Entries 3, 4, 5, 6, 7). However, the best conditions were in benzene (entry 7).

Isolation of *Z*-enone **7.033** appeared to be problematic since it slowly isomerized on silica into the unwanted *E*-enone **7.034** along with some aldehyde. The aldehyde probably comes from silica-catalyzed retro-aldol of the *Z*-enone **7.033** or the *E*-enone **7.034** catalysed by silica. The identification of both enones was made by ^{1}H-NMR. These data suggest that the Lindlar reduction successfully provided the desired *Z*-enone **7.033** and that the product generated during flash silica purification is most probably *E*-enone **7.034** (Scheme 10).



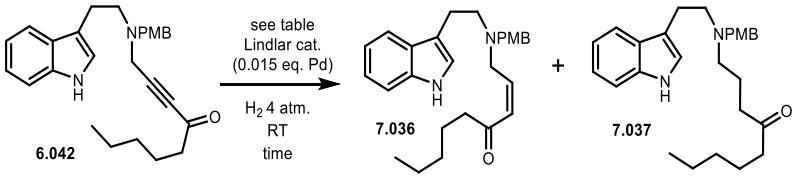
H_A = 6.28 (dt, *J*= 11.4, 5.6 Hz, 1H) H_C = 6.78 (dt, J= 16.0, 6.0 Hz, 1H) H_E = 6.70 (dt, J= 16.0, 6.9 Hz, 1H)
H_B = 6.11 (dt, *J*= 11.6, 2.2 Hz, 1H) H_D = 6.70 (dt, J= 16.1, 1.5 Hz, 1H) H_F = 6.01 (dt, J= 16.0, 1.4 Hz, 1H)

Scheme 10: Enones

However, since the purification by silica gel was impossible in the classic conditions, a small quantity of quinoline from the Lindlar reduction contaminated the product (approximately 10 % of the weight).

b. Lindlar reduction of ynone 6.042

The same protocol was used on ynone **6.042**. Two major products could be expected the desired *Z*-enone **7.036** and the saturated ketone **7.037** (Scheme 11) and (Table 2).



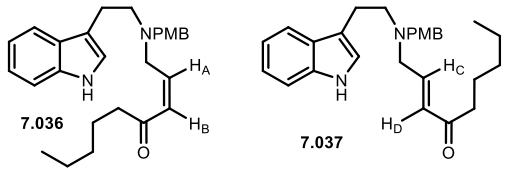
Scheme 11: Lindlar reduction of ynone 6.042

Entry	Solvent	Quinoline (eq.)	Time	Ratio		
				6.042 (%)	7.036 (%)	7.037 (%)
1	Tol	/	12h	/	/	>95
2	Benz.	0.5	1h	/	90	10

Table 2: Lindlar reduction of ynone 6.042

Toluene used as solvent without quinoline provided the saturated product **7.037** in half a day (Entry 1). And as previously reported, benzene and half an equivalent of quinoline appeared to be the best conditions so far to obtain **7.036** (Entry 2).

Similar to the previous results, the NMR data of *Z*-enone **7.036** was compared to *E*-enone **7.037** which is probably the side product created during flash silica purification (Scheme 12).

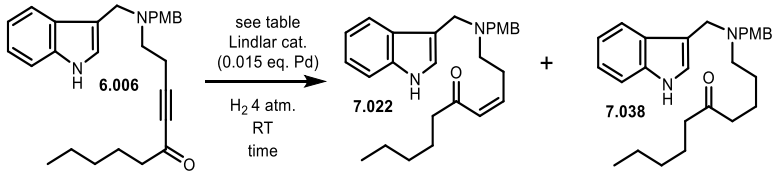


H_A = 6.27 (dt, *J*= 11.6, 5.5 Hz, 1H) H_C = 6.78 (dt, J= 16.0, 5.9 Hz, 1H)
H_B = 6.18 (dt, *J*= 11.6, 2.0 Hz, 1H) H_D = 6.20 (dt, J= 16.0, 1.4 Hz, 1H)

Scheme 12: *E* and *Z*-enones

c. Lindlar reduction of ynone 6.006

The Lindlar protocol was further applied to ynone **6.006**. Two products are expected, the *Z*-enone **7.022** and the saturated ketone **7.038** (Scheme 13) and (Table 3).



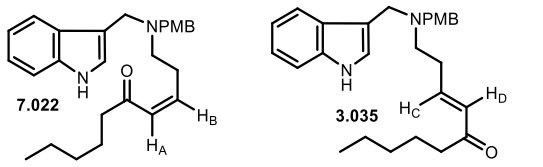
Scheme 13: Lindlar reduction of ynone 6.006

Entry	Solvent	Quinoline (eq.)	Time	Ratio		
				6.006 (%)	7.022 (%)	7.038 (%)
1	Tol	/	12h	/	/	>95
2	Benz.	0.5	1h	/	90	10

Table 3: Lindlar reduction of ynone 6.006

Toluene used as solvent without quinoline provided the saturated product **7.038** in 12 hours (Entry 1). And as previously reported, benzene and a half equivalent of quinoline appears to be the best conditions so far to obtain **7.022** (Entry 2).

The NMR data of the new product **7.022** was compared to our *E*-enone **3.035** (Scheme 14).

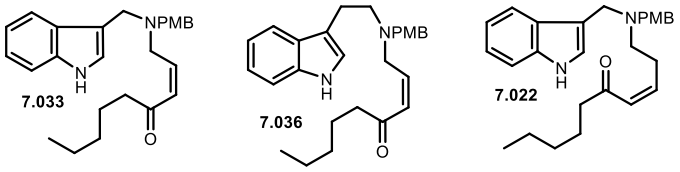


H_A = 6.12 (dt, *J*= 11.4, 1.5 Hz, 1H)
H_B = 6.04 (dt, *J*= 11.5, 6.7 Hz, 1H)
H_D = 6.01 (dt, J= 16.0, 1.4 Hz, 1H)
H_C = 6.70 (dt, J= 16.0, 6.9 Hz, 1H)

Scheme 14: *Z* and *E*-enones

3. Polycyclization tests on *Z*-enones

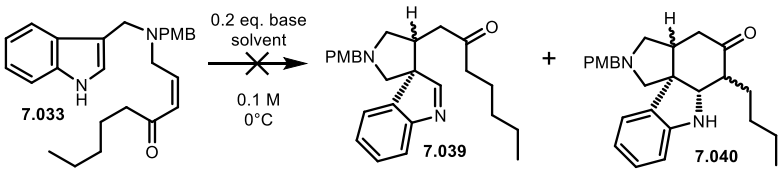
With the three desired *Z*-enones **7.033**, **7.036** and **7.022** in hands polycyclization tests could be started (Scheme 15).



Scheme 15: Z-enones

a. Tests on *Z*-enone 7.033

Throughout these tests, we were hoping to prove the proposed hypotheses and synthesize intermediate **7.039** or tetracycle **7.040** (Scheme 16).



Tested conditions: **A** = *t*BuOK, THF; **B** = *t*BuOK, Toluene; **C** = *t*BuOLi, THF; **D** = *t*BuOLi, Toluene; **E** = DBU, THF; **F** = DBU, CH_3CN; **G** = TMG, THF; **H** = TMG, CH_3CN.

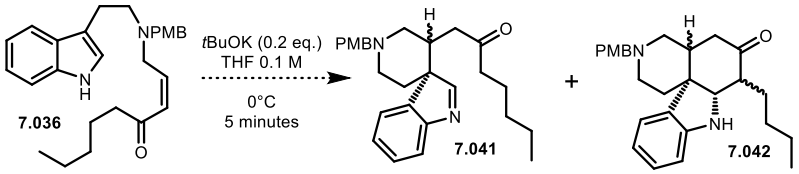
Scheme 16: Polycyclization tests

The conditions for classic polycyclization were applied and led to degradation (Entries **A**, **E** and **F**). Entry **B** was a test reaction to obtain the spiro indolenine **7.039**, however, it was unsuccessful. The use of lithium tert-butoxide provide solely degradation (Entries **C** and **D**). Finally, the use of TMG did not provide the expected products (Entries **G** and **H**).

So far, the cyclization into [5,6] tetracycle **7.040** was unsuccessful.

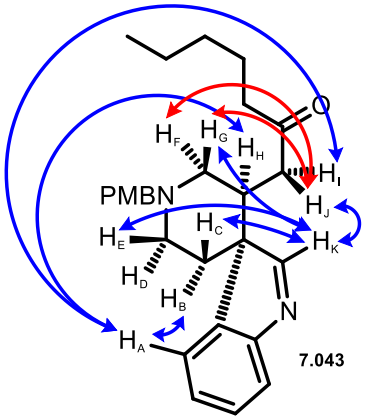
b. Polycyclization tests on *Z*-enone 7.036

Through this cyclization we expected to obtain to products, spiro indolenine intermediate **7.041** and tetracycle **7.042** (Scheme 17).



Scheme 17: Polycyclization conditions of enone 7.036

After 5 minutes of reaction a new product was observed by TLC and was purified by flash column chromatography to afford 25% of the spiro indolenine **7.041**. This was a very big surprise as spiro-indolenine should be highly reactive compounds. The conformation was established by NOESY (There is no difference between the blue arrows and the red arrows, it's just to avoid confusion with overlap of arrows) (Scheme 18).

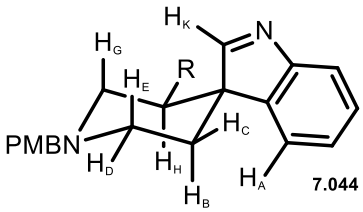


Scheme 18: NOESY of intermediate 7.043

As there is no up and down in molecule, we need to fix them to simplify the following part. The hydrogen H_A will be a reference for the bottom part of the molecule since it need to be below the new 6-membered ring. And the hydrogen H_K will be a reference of the top part of the molecule since it should point up. H_A is able to interact with H_B, H_H, and H_I, this observation should place those three hydrogens down. H_K can spot H_C, H_E,

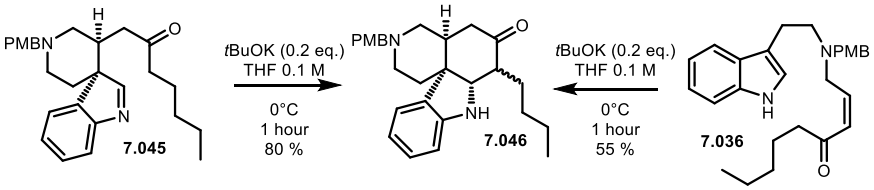
H_G, and H_J, these data make them point up. Finally, H_J is able to notice H_F and H_G (Scheme 18).

Based on these nuclear Overhauser effects, the following relative configuration **7.044** was proposed. The freely rotating side chain was changed for "R" to make the drawing easier. Proton H_A correlates with H_B and H_H. The proton H_K can spot H_C, H_E, H_G. And finally, H_D cannot observe any hydrogen. This conformation fits well enough with the data and is probably one of the conformations in $CDCl_3$. As we can observe, H_H needs to be down to correlate with H_A, this evidence is a good point for hypotheses 2 and 3 (Scheme 19).



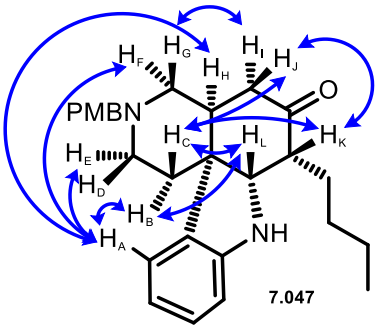
Scheme 19: Conformation of intermediate

This intermediate should rearrange into the desired product to demonstrate hypothesis 1. The molecule **7.045** was resubmitted to the polycyclization conditions and the corresponding reaction was also tested with the *Z*-enone for a longer time than 5 minutes (Scheme 20).



Scheme 20: Polycyclizations

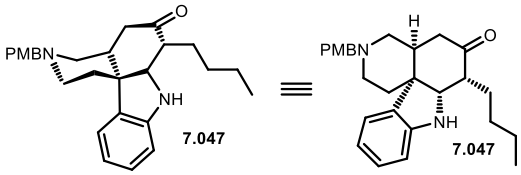
In both cases, a new product was observed, isolated and characterized by NOESY (Scheme 21).



Scheme 21: NOESY of tetracycle

As explained *vide supra*, H_A will be the down hydrogen and H_L will be the hydrogen up. In this molecule, we can observe many strong correlations by NOESY since the structure possesses only few degrees of freedom. The hydrogen H_A can interact with H_B, H_E, H_F and H_H, which make them down. The hydrogen H_C can spot H_L and H_K and H_J. Finally, H_L sees H_B, H_K can observe H_J and H_I can interact with H_G. Unfortunately, if H_K can detect upper hydrogens H_C and H_J it means that the side chain is pointing down and H_K is up. By ^1H NMR the coupling constant H_L-H_K is around 4 Hz which is a standard coupling for *cis*-vicinal hydrogens in a 6-membered ring.

The structural conformation deduced by NOESY in $CDCl_3$ is chair-chair and could explain all observed correlations (Scheme 22).

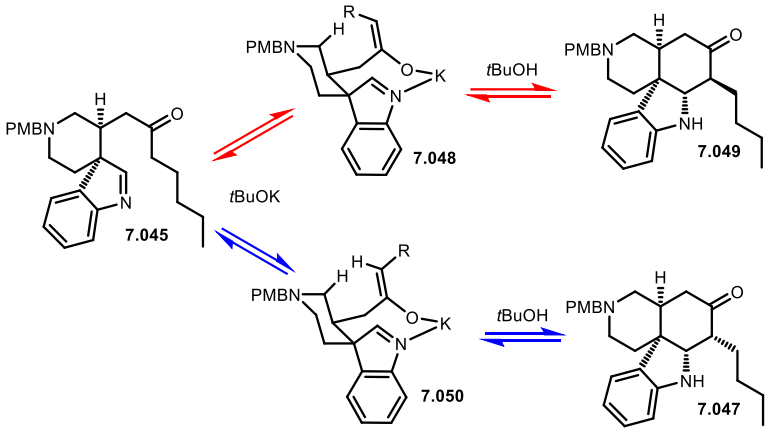


Scheme 22: Conformation

Hypothesis 1 appears to be incorrect, since we have the intermediate **7.045** and the tetracycle **7.047** we could reformulate this hypothesis.

c. Second cyclization hypothesis

Deprotonation of ketone **7.045** could lead to two enolates, **7.048** and **7.050**. These enolates could afford respectively the tetracycles **7.049** and **7.047** (Scheme 23).

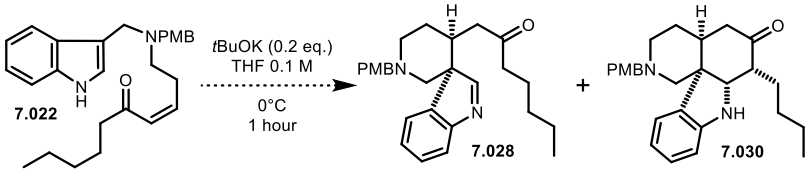


Scheme 23: Enolates and targets

In hypothesis 1, we expected a boat conformation for the 6-membered ring. Unfortunately, the observation made by NOESY suggest the intermediate to be in chair conformation. With a chair in **7.048** and **7.050**, there is a significant difference of steric hindrance. The desired product **7.049** should come from the *E*-enolate **7.048** which possesses an H-R steric hindrance. The other enolate **7.050** possesses an H-H steric hindrance, and it should be smaller. According to the product we obtain and to the difference of energy in the transition state, the blue path is favoured.

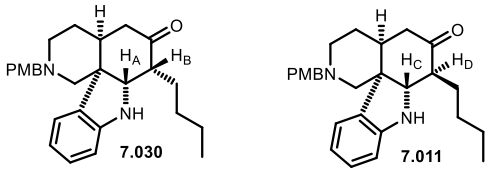
d. Polycyclization test on *Z*-enone 7.022

The conditions were tested on the last *Z*-enone. We expected to obtain spiro indolenine **7.028** or tetracycle **7.030** (Scheme 24).



Scheme 24: Cyclization of Z-enone 7.022

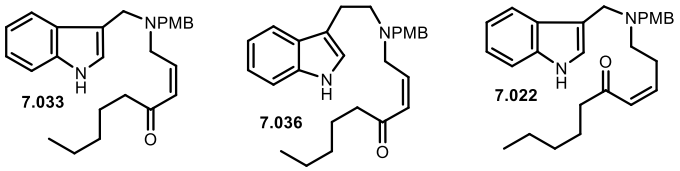
The outcome of the reaction was slightly different than the expected results as two products were obtained. Both possess a similar polarity by TLC and by column chromatography. No indolenine was detected so it cannot be **7.028**. ^{1}H NMR revealed two new sets of resonances isolated from the rest of the signals. Two doublets, the first around 4.03 (d, *J* = 8.0 Hz, 1H) and the second just next to it at 3.96 (d, *J* = 3.4 Hz, 1H). No starting material was left in the crude NMR spectrum and the rest of the features were very similar to the previously reported tetracycles. An 8 Hz coupling constant could come from a *trans*-vicinal H_C-H_D when a 3.4 Hz coupling constant could come from a *cis*-vicinal H_A-H_B. Unfortunately, those are just speculations since we could not properly separate the two products (Scheme 25).



Scheme 25: Speculations of the stereochemistry

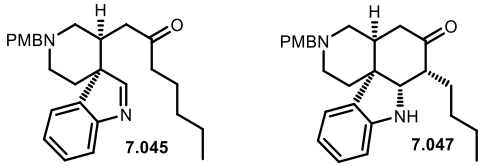
4. Conclusions

The Lindlar reduction appeared to be a nice way to synthesize *Z*-enones starting from ynones and allowed access to polycyclization tests on **7.033**, **7.036** and **7.022** (Scheme 26).



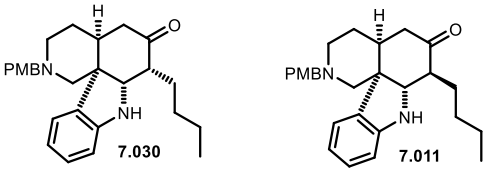
Scheme 26: *Z*-enones

These tests were not successful for **7.033**. However, intermediate **7.045** and tetracycle **7.047** were fully characterised from **7.036** as starting material (Scheme 27).



Scheme 27: Interesting products

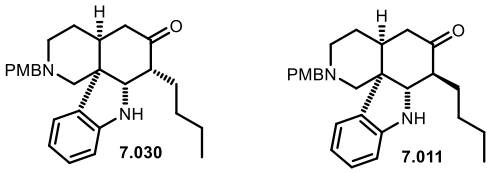
Amongst all three hypotheses proposed in the beginning of this chapter, two of them were demonstrated successful so far (see pages 159 and 160). Unfortunately, the first hypothesis was proven to be untrue or at least incomplete. The last reaction of this chapter could have changed this, however, the two new products **7.030** and **7.011** are just speculations so far until they are purified (Scheme 28).



Scheme 28: Speculations

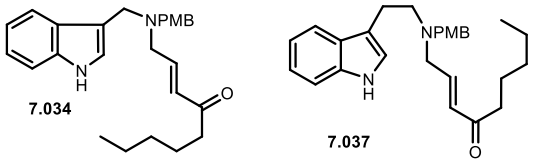
5. Perspectives

The most obvious perspective is the purification of the tetracycle(s) **7.030** and **7.011** using semi-preparative HPLC, preparative HPLC or paper chromatography (Scheme 29).



Scheme 29: Potential tetracycles obtained

Isomerisation from *Z*-enone to *E*-enone should be improved and polycyclization tests should be done on **7.034** and **7.037**. To analyse the outcome and add more evidence to our hypotheses (Scheme 30).

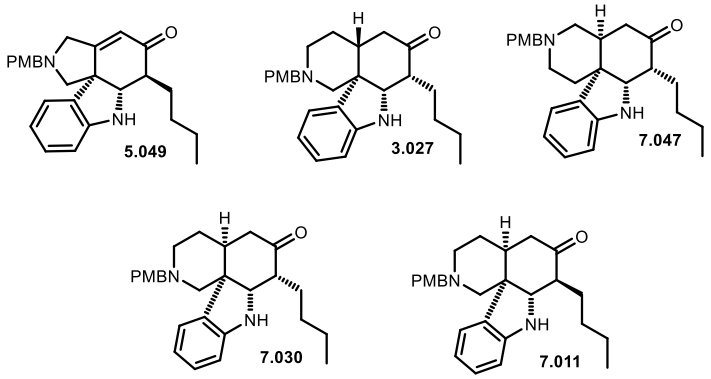


Scheme 30: *E*-enones

Chapter VIII

Derivatizations

Through the previous chapter V, VI and VII various tetracycles were produced **5.049**, **3.027**, and **7.047**. Speculations were made about **7.030** and **7.011** but without full characterization (Scheme 1).

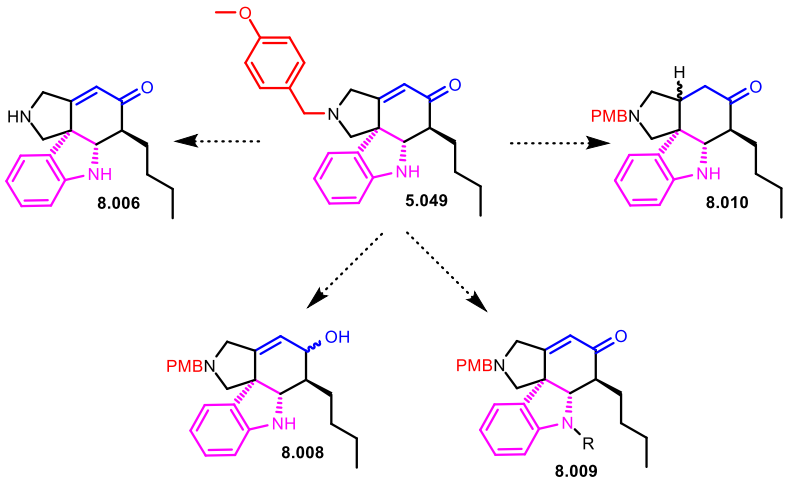


Scheme 1: Formed and speculated tetracycles

This chapter will be devoted to the extension of the library of tetracycles through derivatization. The point is to improve the probability to find bioactive molecules among them. In addition to those modifications, we were expecting to have control of the diastereoselectivity of these reactions due to the rigid scaffold of the molecule.

1. Modification of tetracycle 5.049

There are different functionalities on molecule **5.049** including an indoline (in pink), vinyl ketone (in blue) and a PMB (in red). The PMB can undergo a hydrogenolysis to **8.006**. The vinyl ketone could be a precursor of alcohol **8.008** or a precursor of saturated ketone **8.010**. Finally, alkylation of indolenine to **8.009** offers a further option for derivatization (Scheme 2).

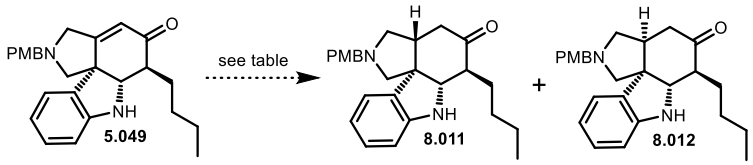


Scheme 2: Modification of tetracycle

The reduction of the vinyl ketone should be easier than alkylation and PMB removal. And reduction of the double bond could possibly lead toward the desired isomer. So, it will be our first investigation.

a. Reduction of the double bond in 5.049

The reduction of vinyl ketone **5.049** to the *trans*-fused ketone **8.011** or the *cis*-fused ketone **8.012** could be obtained by any Stryker type reductant[1] or by hydrogen transfer (Scheme 3) and (Table 1).



Scheme 3: Reduction of double bond

Entry	Conditions	Outcome
1	$[(PPh_3)CuH]_6$, benzene, RT	**5.049**
2	$Cu(OAc)_2$, $P(Oi\text{-}Pr)_3$, $Me(EtO)_2SiH$, tol, RT	**5.049**
3	$Cu(OAc)_2$, PPh_3, $Me(EtO)_2SiH$, tol, RT	**5.049**
4	$Pd(OH)_2$, H_2 (4 atm.), MeOH, RT	New compound

Table 1: Reduction of double bond

The classic reduction of unsaturated ketone with Stryker reagent[2] or modified Stryker reagent[3] did not provide any new compounds and afforded a full recovery of starting material (Entries 1, 2 and 3). A new compound was observed with hydrogenation by palladium hydroxide[4] and hydrogen (Entry 4).

The determination of the diastereoselectivity was made by NOESY. Many interactions could be observed, and to simplify, the PMB and the side chain correlations won't be showed (Scheme 4).

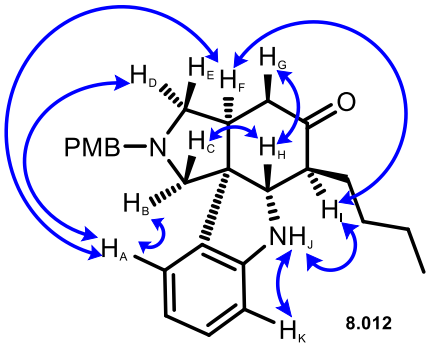
---

[1] (a) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc*. **1988**, *110*, 291. (b) Bezman, S. A.; Churchill, M. R.; Osborn, J. A.; Wormald, J. *J. Am. Chem. Soc*. **1971**, *93*, 2063.

[2] Riant O. "Copper(I) hydride reagents and catalysts" Patai's Chemistry of Functional Groups, **2011**, John Wiley & Sons.

[3] Pelss, A.; Kumpulainen E. T. T.; Koskinen A. M. P. *J. Org. Chem.* **2009**, *74*, 7598.

[4] Pearlman's catalyst

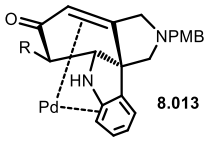


Scheme 4: NOESY of saturated tetracycle

As in chapter VII, the reference needs to be fixed as there is no up and down in molecule. The hydrogen H_A will be the reference for down and H_H will be the reference for up. Hydrogen H_A can see H_B, H_D and H_F which make them down. Hydrogen H_H can interact with H_C and H_G which make them up. H_I can see H_F and H_J, Finally, H_J can detect H_K. Hydrogen H_J does very nice correlations by NOESY however since it's a labile hydrogen, it won't be taken in consideration.

According to these data, the product is *cis*-fused, and the side chain is up. Hydrogen H_F would not be able to interact with H_A and H_I if it was up.

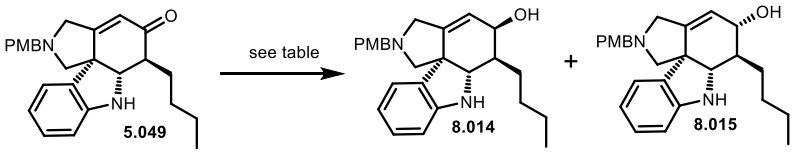
For the first time in this project, the correct isomer could be isolated and characterized. The speculated mechanism for this reduction is based on coordination of palladium to the indoline moiety as the most electron rich system in the molecule. Finally, the speculation about chelation with indoline and the double bond should lead to the intermediate **8.013** (Scheme 5).



Scheme 5: Palladium coordination

b. Reduction of the ketone

There are two possible results in the ketone reduction, alcohol **8.014** and **8.015**. Luckily, both are interesting as selective extension of library (Scheme 6) and (Table 2).



Scheme 6: Reduction of ketone

Entry	Reducing agent	Solvent	T (°C)	Ratio (%)	
				8.014	8.015
1	DIBAL-H (2.5 eq.)	Toluene	-78	10	90
2	DIBAL-H (2.5 eq.)	DCM	-78	10	90
3	DIBAL-H (2.5 eq.)	THF	-78	40	60
4	$NaBH_4$ (2 eq.)	MeOH	0	15	85
5	$NaBH_4$ (2 eq.)	EtOH	0	20	80
6	$NaBH_4$ (1.3 eq.), $CeCl_3$ (2 eq.)	MeOH	0	80	20
7	$NaBH_4$ (1.3 eq.), $CeCl_3$ (2 eq.)	MeOH	0	70	30
8	$NaBH_4$ (1.3 eq.), $CaCl_2$ (2 eq.)	MeOH	0	20	80

Table 2: Reduction of ketone

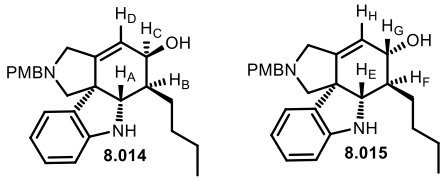
The use of DIBAL-H[5] (Entries 1, 2 and 3) provides alcohol **8.014** as the major product. Sodium borohydride provides the same results with alcohol **8.014** as major product (Entries 4 and 5). Classical Luche[6] reduction (Entries 6 on 0.1 g scale and 7 on 0.5 g scale) affords the other alcohol **8.015** as the

[5] Ziegler, K.; Martin, H.; Krupp, F. *Justus Liebigs Annalen der Chemie* **1960**, *629*, 14.
[6] Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.

major product. The modified Luche [7] conditions using calcium chloride provides the opposite outcome from the use of cerium chloride (Entry 8).

Both alcohols were separated flash column chromatography and fully characterized. The determination of the diastereo-relationship was not easy as NOESY appeared to be inefficient on these compounds. It is mostly due to the fact that the newly formed C-H bond is too far away from the rest of the molecule to make spatial interactions.

At the time of characterization, we realized that the hydrogens A-B-C-D were really different than E-F-G-H. Since these molecules could possess various conformations due to the 5 substituents on the cyclohexene ring, the decision was made to estimate the stable conformations of those molecule **8.014** and **8.015** *via* calculations (Scheme 7).



Scheme 7: epimers of alcohols

The first calculation was made on **8.014** and based on one thousand iterations the lowest energy value is 384.0497 kJ/mol. Here, different effects and angles could be observed. There is a strong anomeric effect between σ C-H_B and σ* C-O. Hydrogens H_A and H_B are presumably axial. Finally, the angle between H_C and H_D is 47.9° and according to Karplus-Bothner-By equation[8], H_D should be a doublet with a coupling constant between 4.5 and 6 Hz (Figure 1).

[7] Fujii, H.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1991**, *20*, 1847.
[8] (a) Karplus, M. *J. Chem Phys*. **1959**, *30*, 11. (b) Karplus, M. *J. Am. Chem. Soc*. **1963**, *85*, 2870. (c) Bothner-By A. A. *Adv. Magn. Reson.* **1965**, *1*, 195.

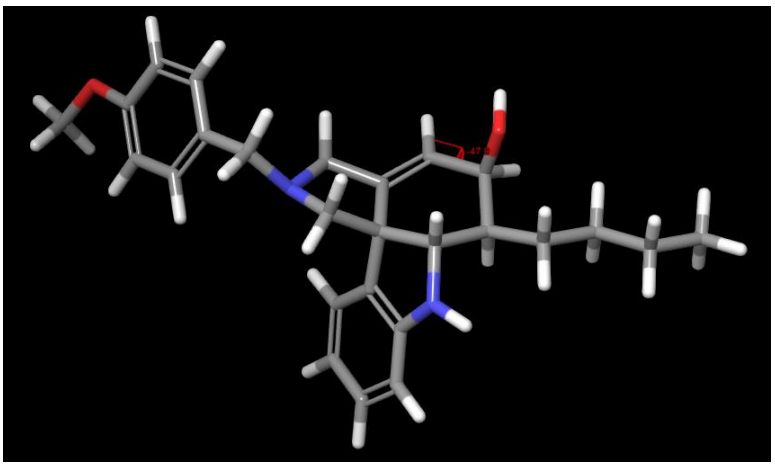


Figure 1: Alcohol 8.014 by calculation

The calculations were also made for the second alcohol **8.015**. An issue was encountered as the lowest and the second more stable conformations have two very distinct conformations (Figure 2) and (Figure 3).

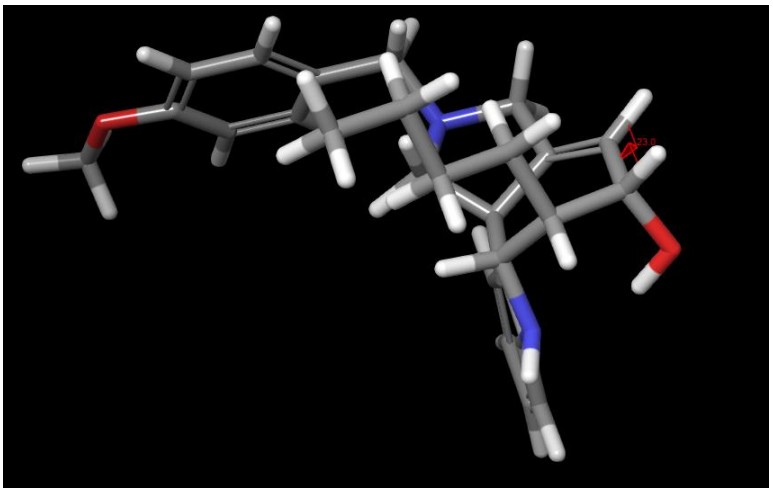


Figure 2: Lowest energy for alcohol 8.015

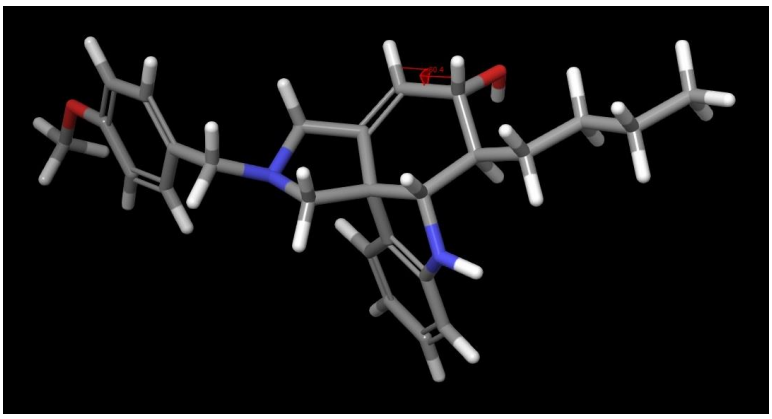
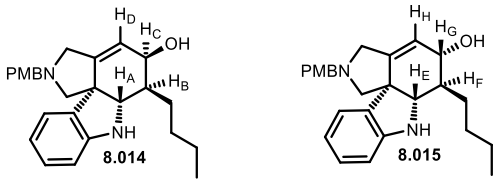


Figure 3: Second more stable conformation

Both conformations were compared to the ^{1}H NMR. The first conformation of **8.015** is 383.0155 kJ/mol and possesses an N-H-O hydrogen bond. However, the nitrogen lone pair cannot be devoted completely to this hydrogen bond because it's an indoline and the electrons are shared in the aromatic ring. The angle between H_G and H_H is 23.0° which should make H_H as a doublet with a coupling constant of 8-10 Hz (Figure 2) and (Scheme 8).

The second conformation of **8.015** is 383.5075 kJ/mol. The dihedral torsion angle H_G-H_H is 60.4° which makes H_H a doublet with a coupling constant of 3-4 Hz. Hydrogens E-F-G are all three axial and should be more shielded due to this position (Figure 3) and (Scheme 8).



H_A = 3.86 - 3.76 (m, 1H)
H_B = 2.08 - 2.00 (m, 1H)
H_C = 4.21 - 4.08 (m, 1H)
H_D = 5.78 (d, *J*= 5.9 Hz, 1H)

H_E = 3.56 (d, J= 6.9 Hz, 1H)
H_F = 1.72 - 1.64 (m, 1H)
H_G = 4.26 - 4.23 (m, 1H)
H_H = 5.61 (dt, *J*= 1.8, 1.6 Hz, 1H)

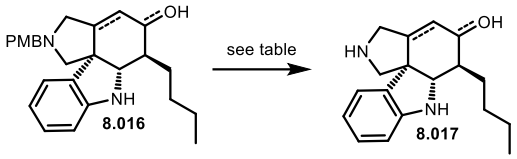
Scheme 8: Determination of diastereoisomer

According to the descriptions *vide supra* **8.014** embodies the β-alcohol. It possesses a 5.9 Hz coupling at H_D corresponding to H_C-H_D coupling estimated between 4.5 and 6 Hz (Correct). At the same time, H_B due to the anomeric effect should be less shielded than H_F, and at the same time H_F should be more shielded than H_B because H_E and H_G sigma donation (Correct). For **8.015**, the most stable conformation needed a coupling constant at H_D or H_H of 8-10 Hz, none of these substrates exhibited such a strong coupling (incorrect). However, in the calculated second most stable conformer, the same coupling constant could be 3 to 4 Hz. In the suspected **8.015** with α-alcohol there is a 1.6 Hz coupling constant for H_H, it's a bit lower than expected (Almost correct).

From now on, we assume that the diastereochemistries are fixed for β-ol-**8.014** and α-ol-**8.015**.

c. Deprotection of PMB

Several deprotection protocols of PMB were tested on almost every tetracycle in our hands, so to avoid repetition of tables, we will schematize it as **8.016** (Scheme 9) and (Table 3).



Scheme 9: Deprotection

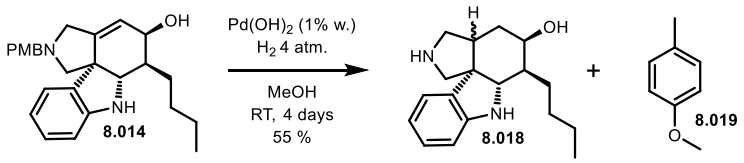
Entry	Reagent	Solvent	T°C	Outcome
1	CAN	CH_3CN/H_2O	RT	Decomposition
2	DDQ	DCM/H_2O	RT	Decomposition
3	TFA	DCM	RT	**8.016**
4	TFA	DCE	Reflux	**8.016**
5	$Pd(OH)_2$ + NH_4HCO_2	MeOH	Reflux	Decomposition
6	$Pd(OH)_2$ + formic acid	MeOH	Reflux	Decomposition
7	$Pd(OH)_2 + H_2$	MeOH	RT	New product

Table 3: Deprotection

Standard deprotection of PMB (Entries 1, 2, 3 and 4) appears to be unsuccessful, the oxidation process led to decomposition and the acidic to starting material recovery. Hydrogenolysis was also unsuccessful until a new product was observed (Entries 5, 6 and 7).

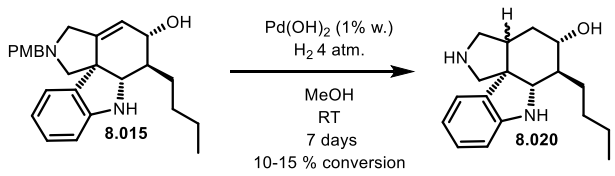
The reaction was carried out on **8.014** which was converted to **8.018** in 4 days. *p*-Methoxy-toluene could be observed by ^1H NMR. So far, there is no certainty about the diastereoselectivity at the junction. Both, the alcohol

or the indolenine could direct the palladium catalyst to approach from both faces (Scheme 10).



Scheme 10: PMB removal

The same reaction was tested on **8.015** but appeared to be extremely slow with 10 to 15% conversion in a week. Due to the very small amount of product and the poor quality of the reaction, poisoning of the catalyst was suspected. The palladium could be trapped between α-oxygen and α-nitrogen, in a 1,3-diaxial conformation to the extent of our knowledge (Scheme 11).



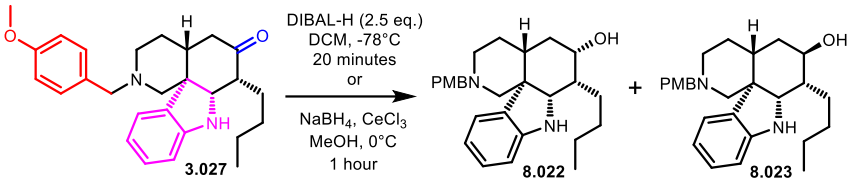
Scheme 11: deprotection of 8.015

2. Modification of [6,6] tetracycle 3.027

The [6,6] tetracycle **3.027** based on SGAP possesses an indoline (in pink) a ketone (in blue) and a PMB (in red). As explained *vide supra*, there are many downstream modifications available for this class of substrates.

a. Reduction of the ketone

We will first focus on the reduction of the ketone (Scheme 12)



Scheme 12: Reduction of ketone 3.027

Both conditions for the reduction of ketone were tested and only one diastereoisomer was obtained. The crystal structure of **3.027** (*Cf.* chapter VI) indicates a chair-boat conformation in solid phase. This makes the top face extremely easy to access and should provide the α-alcohol **8.022**.

To support this statement and also to improve the quality of our previous calculations, the conformation stability of ketone **3.027** will be estimated and compared to the crystal structure (Figure 4).

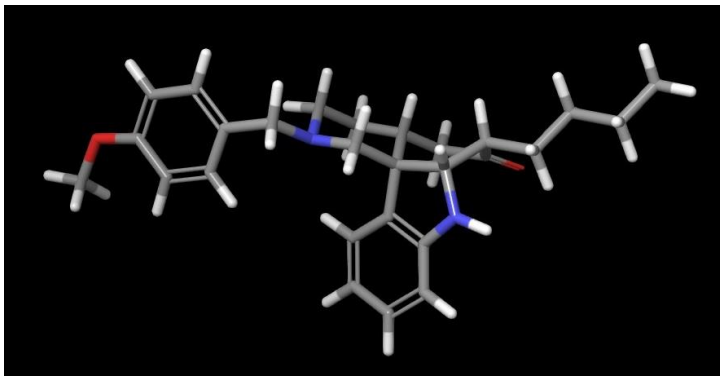


Figure 4: Calculation for ketone 3.027

The calculated structure and the crystal structure are extremely alike (*Cf.* Chapter VI). This information provides more credibility of the previous calculations.

Fortunately, crystals of **8.022** could be obtained by slow evaporation of *n*-hexane. The conformation in solid phase appeared to be chair-boat, just like the ketone and as expected the reduction happened from the top face to furnish the α-alcohol **8.022**. Once again, we can confirm the fused-*trans*-junction and the *cis*-junction between indolenine and the side chain (Figure 5).

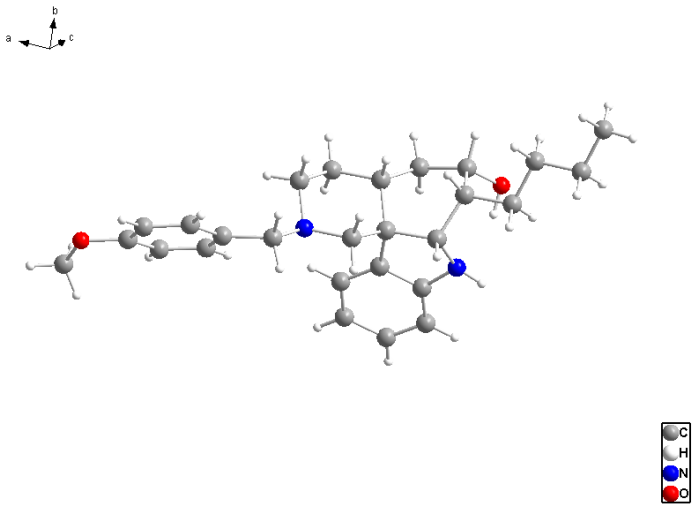
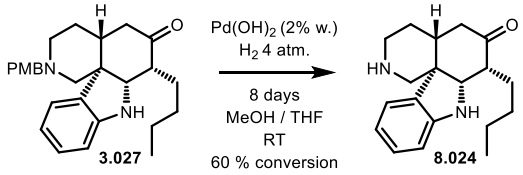


Figure 5: X-Ray structure of alcohol 8.022

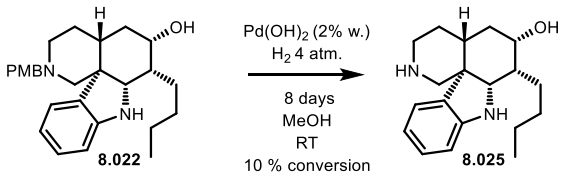
b. Deprotection of the PMB

The deprotection was tested on the ketone **3.027** to obtain **8.024**. The conversion was about 60% in 8 days (Scheme 13).



Scheme 13: Deprotection of ketone

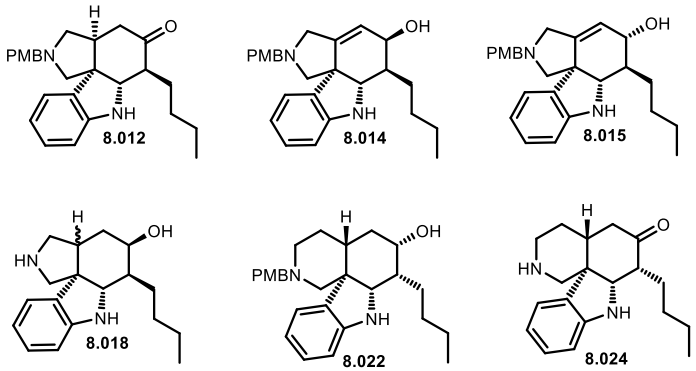
And finally, the same reaction was tested on alcohol **8.022**. The same behaviour in **8.015** was observed, an extremely slow conversion into the target molecule **8.025**. The suspicion of poisoning of palladium catalyst increased as both products **8.015** and **8.022** got a similar feature. The 6 membered ring moiety (right part) possesses a 1,3 diaxial aminol. Due to the small quantities of available material, this product has not been fully characterized yet (Scheme 14).



Scheme 14: Deprotection of alcohol 8.022

3. Conclusions

In this chapter, 6 new tetracycles were synthetized inclusive of, a saturated ketone **8.012**, allylic alcohols **8.014** and **8.015**, deprotected alcohol **8.018**, alcohol **8.022** and deprotected ketone **8.024** (Scheme 15).



Scheme 15: New tetracycles

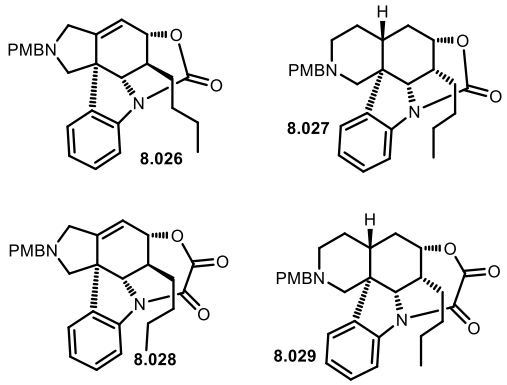
Most of them were obtain as a single diastereoisomer such as **8.012**, **8.018** and **8.022**. Alcohols **8.014** and **8.015** could be synthetized from the same molecule by the ratio will change depending on the reducing agent used.

Saturated ketone **8.012** appears to be the desired isomer for the synthesis of [5,6] indole manzamine.

X-Ray diffraction confirmed the structure of alcohol **8.022**.

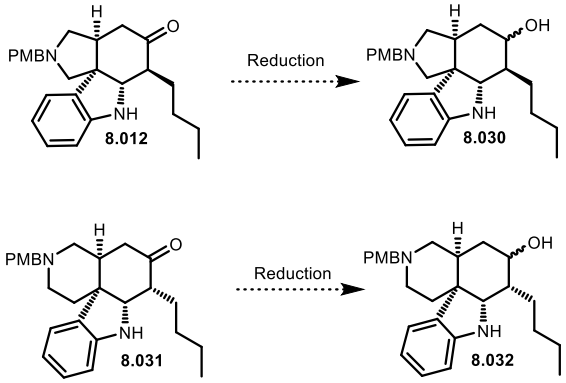
4. Perspectives

The use of CDI or oxalyl chloride on **8.015** and **8.022** could lead to the synthesis of cyclic carbamates **8.026** and **8.027** or amide-ester **8.028** and **8.029** (Scheme 16).



Scheme 16: Use of CDI or oxalyl chloride

Reduction of ketones **8.012** and **8.031** to the corresponding alcohol **8.030** and **8.032**. Thereby extending even further the landscape of available derivatives (Scheme 17).



Scheme 17: Reduction of ketone

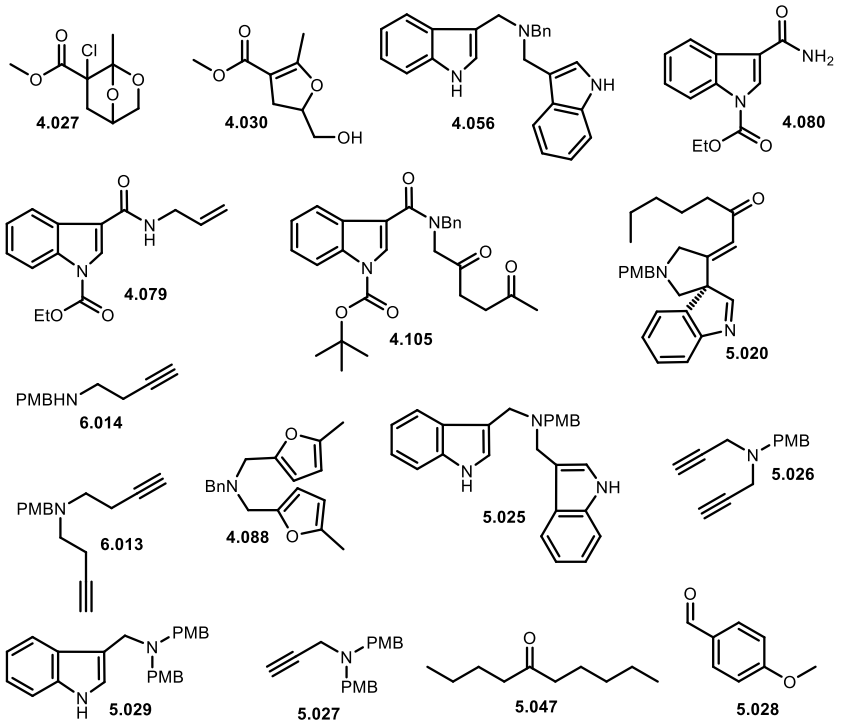
Chapter IX

Conclusions & Perspectives

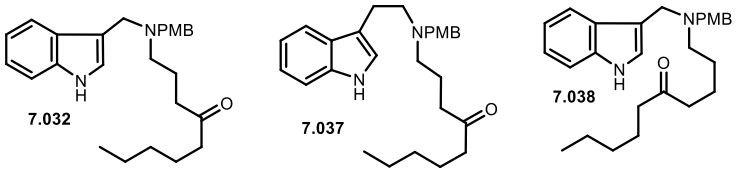
1. Conclusions

a. Side products

Throughout this thesis, many side products were characterized, and the synthesis pathway was adapted to avoid them or to reduce the obtained quantity. Most of them are new for the literature except **6.014**, **4.088**, **5.047** and **5.028** (Scheme 1) and (Scheme 2).



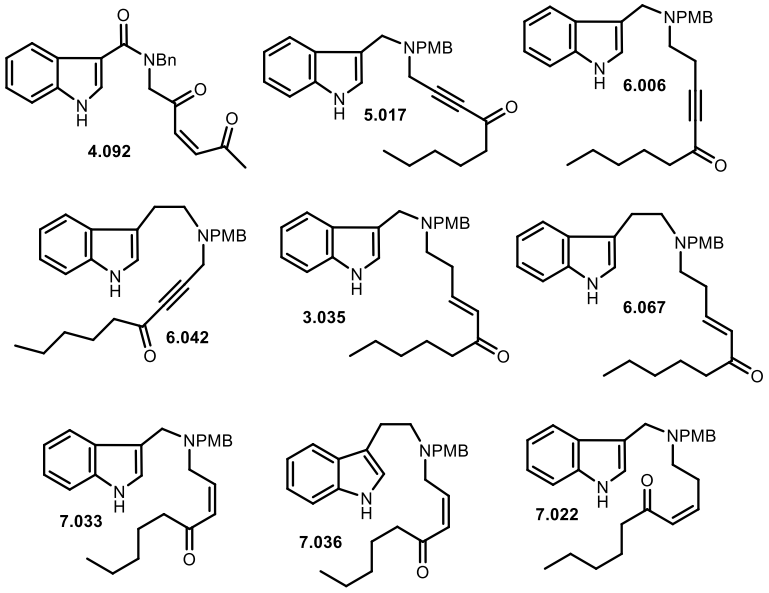
Scheme 1: Side products part 1



Scheme 2: Side products part 2

b. Precursors synthetized

A total of 9 polycyclization precursors were synthesized based on different functions such as ene-dione **4.092**, ynone **5.017**, **6.006** and **6.042**, *E*-enone **3.035** and **6.067** or *Z*-enone **7.033**, **7.036** and **7.022** (Scheme 3).

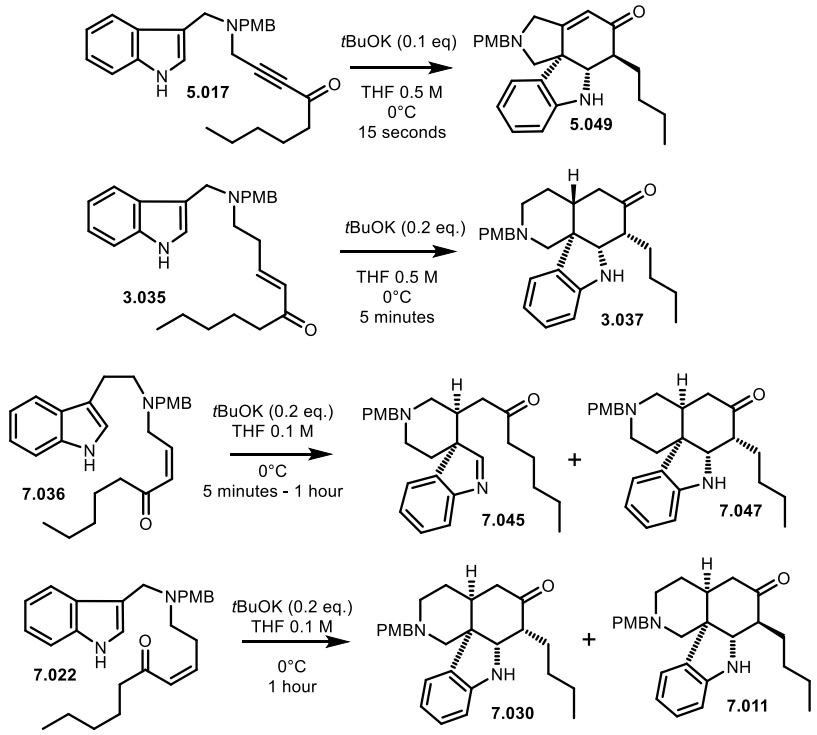


Scheme 3: Precursors

Among these 9 precursors only **3.035** was described before by our group.

c. Polycyclizations

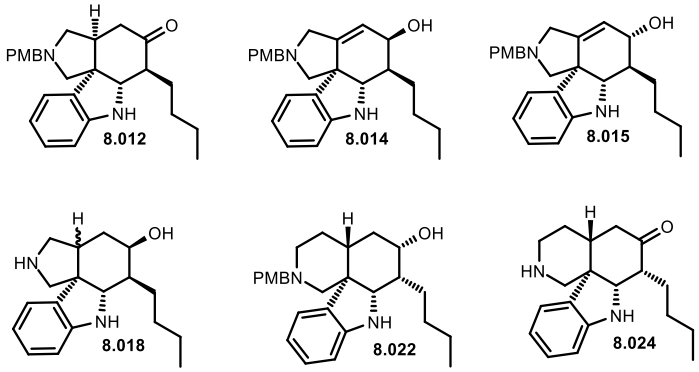
Attempts to cyclize these precursors to the desired tetracycles using an anionic polycyclization methodology were investigated. Four of them cyclized so far, many mechanistic speculations were proposed to explain the obtained results. The final cumulated observation about all those precursors is that the size of the first synthetized ring is related to the Michael acceptor function in the precursor (Scheme 4).



Scheme 4: Polycyclizations

d. Derivatizations & bioactivities

To extend the library of compounds, some diastereo-controlled derivatisations were made (Scheme 5).



Scheme 5: Derivates

e. Completion of objectives

The main objective of this thesis was to develop a short way toward tetracycles using a new methodology of anionic polycyclization. Ynone precursor and *E*-enones were cyclized in 5 steps overall and *Z*-enones in 6 steps.

→ DONE

The secondary objectives were:

Use of cheap starting materials → DONE

Check for bioactivities of the new compounds → DONE

Obtention the correct diastereoisomer → DONE

Finishing the synthesis of indole-manzamine → In progress

2. Perspectives

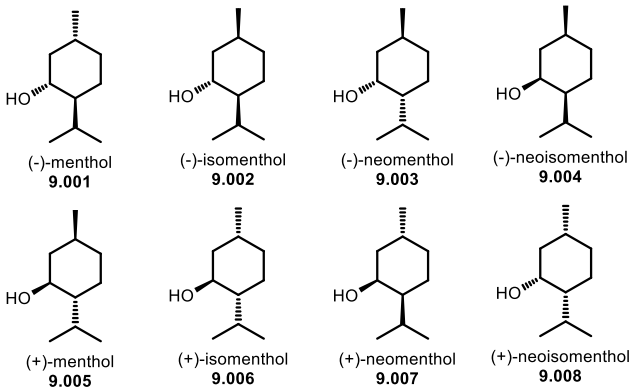
Due to the fact that there are few perspectives at the end of the chapter IV, V, VI, VII, and VIII. Those final perspectives will not be a compilation but additional possibilities.

a. Asymmetric polycyclization

So far, there are two catalysts able to perform these reactions, potassium *tert*-butoxide and DBU. Unfortunately, the product is racemic, however, there are substitutes for these bases in the chiral pool to create asymmetric anion polycyclization.

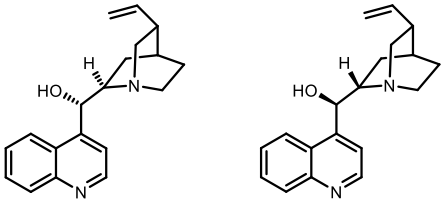
Chiral alcohol

Potassium anion of (-)-menthol **9.001** could be a potent catalyst for this reaction as well as its seven related isomers and they can easily be tested for match-mismatch effect (Scheme 6).



Scheme 6: Menthols

Cinchonine **9.009** and cinchonidine **9.010** could be alternative to menthol (Scheme 7).

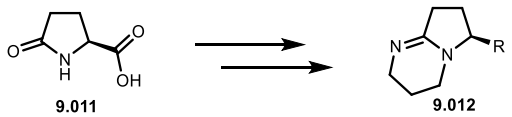


Cinchonine **9.009** Cinchonidine **9.010**

Scheme 7: Cinchonine & cinchonidine

Chiral DBN

Different processes exist to synthesize chiral derivatives of DBN **9.012** from pyroglutamic acid **9.011**. However, the pK_a of DBN is slightly lower than DBU, it could worsen the shot (Scheme 8).[1]



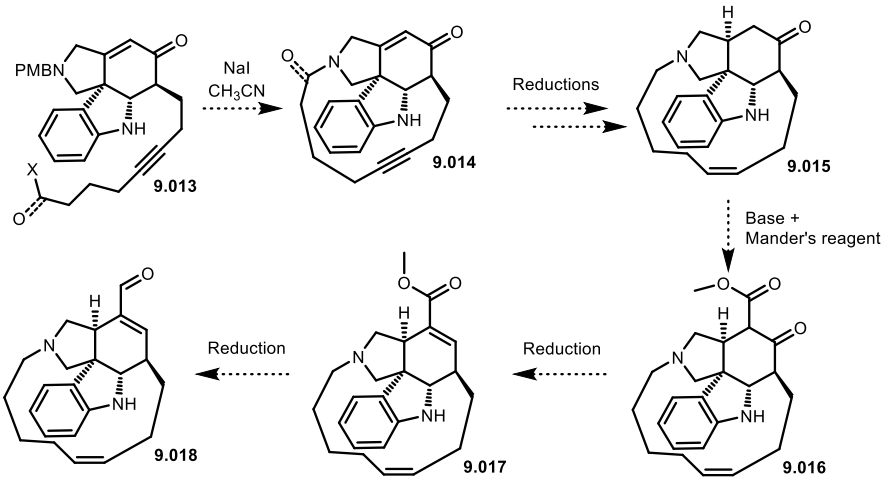
9.011 **9.012**

Scheme 8: Chiral DBN

[1] (a) Kotsuki, H.; Sugino, A.; Sakai, H.; Yasuoka, H. *Heterocycles*, **2000**, *53*, 2561. (b) Ostendorf, M.; Van der Neut, S.; Rutjes, F. P. J. T.; Hiemstra, H. *Eur. J. Org. Chem*. **2000**, 105.

b. Achievement the synthesis

One of the possible ways to finish the synthesis using the [5,6] tetracycle would be to modify the Weinreb amide to obtain **9.013** with an electrophile at the terminus position. Macrocyclisation should be favoured with acyl iodide as electrophile but also with iodide due to the elimination of PMB. Few reductions should be made, we know the hydrogenation of this enone will led to the desired diastereoisomer **9.015**. Then, the following steps come from the total syntheses of manzamine A **1.001**, use of Mander's reagent with a base to get **9.016** then reduction of the ketone into a double bond **9.017**. Finally, DiBAL-H reduction into an indole ircinal derivatives **9.018** should be obtained (Scheme 9).



Scheme 9: Completion of synthesis

Chapter X

Experimental Section

1. Instrumentation

^{1}H and ^{13}C nuclear magnetic resonance spectra were recorded in Belgium on Brucker Avance II-300 spectrometer (^{1}H 300 MHz and ^{13}C 75 MHz) and in Finland on Bruker Avance NEO 400 MHz SmartProbe spectrometer (^{1}H 400 MHz and ^{13}C 100 MHz). ^{1}H chemical shifts are reported in ppm downfield from internal tetramethylsilane (δ = 0 ppm) or $CHCl_3$ (δ = 7.26 ppm) or DMSO (δ = 2.50 ppm). ^{13}C NMR spectra are reported using $CDCl_3$ as the internal standard (δ= 77.16 ppm) or DMSO (δ = 39.52 ppm). If necessary, the structures were confirmed by two-dimensional analysis (COSY, HMQC, HSQC and HMBC). ^{1}H spectra described as follow: chemical shift (multiplicity, coupling constant (Hz), integration, attribution). ^{13}C spectra are described as follow: chemical shift (attribution). Multiplicity is designed as: s = singlet; d = doublet; t = triplet; q = quartet; qui = quintet; sex = sextet; sep = septet; b = broad; and m = multiplet. When the compound presents two diastereotopic signals, the attribution is written X and X' for each signal.

Infrared spectra were recorded by transmittance on Perkin Elmer spectrum one and reported in wavenumber (cm^{-1}). The samples were analysed as thin films deposit by solvent evaporation or as compressed potassium bromide pils.

Low and high-resolution mass spectra were recorded by Mr. Raoul Rozenberg from the Mass Spectrometry Service, Université catholique de Louvain (Belgium) or by Ms. Heidi Meriö-Talvio from the Department of Chemical Technology of Aalto University (Finland).

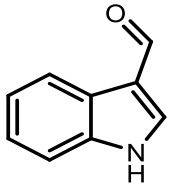
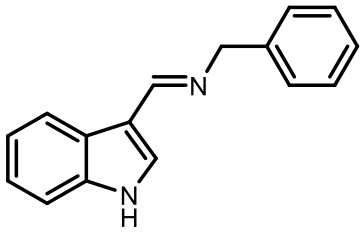
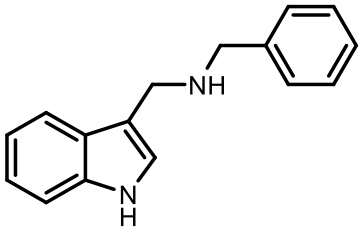
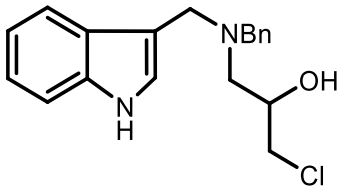
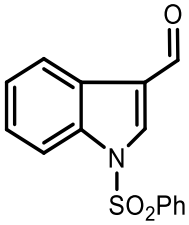
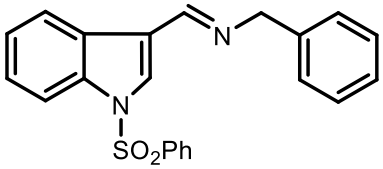
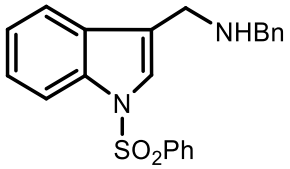
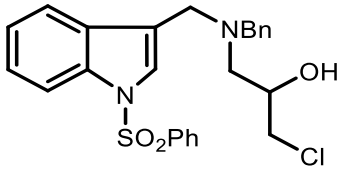
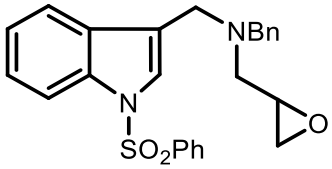
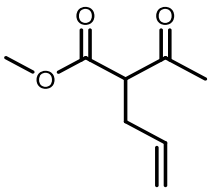
X-ray diffraction were recorded by Dr. Martin Nieger from the Department of Chemistry of University of Helsinki (Finland).

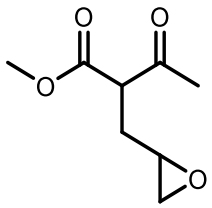
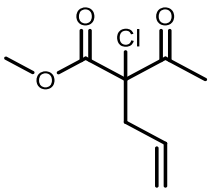
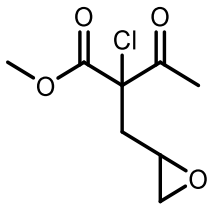
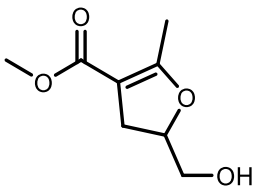
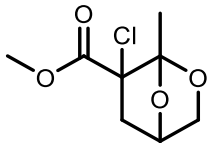
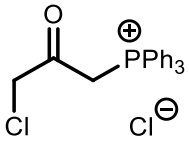
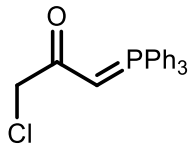
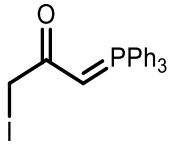
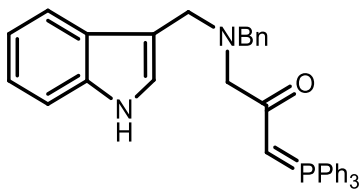
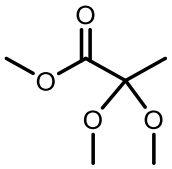
Calculation and conformation analyses were performed by Ari M. P. Koskinen with Macromodel v11.7.

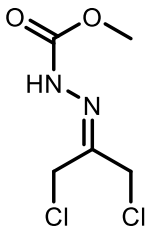
2. Procedure

Unless otherwise noticed, all manipulations were performed under an argon atmosphere using standard glassware. Diethyl ether and tetrahydrofuran were distilled on sodium/benzophenone under argon atmosphere. Dichloromethane, triethylamine, and toluene were distilled on calcium hydride. Solvents used for work-up were of technical grade. Commercial reagents were purchased from Acros, Sigma-Aldrich, ABCR, TCI, Merck or Fluorochem and used as received unless stated otherwise.

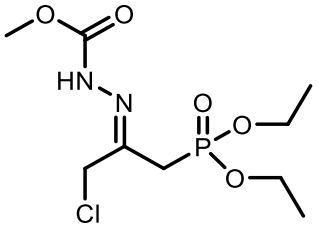
Thin layer chromatographies were performed on Merck Millipore F_{254} silica gel 60 plates (200 µm thickness, aluminium supported). The plates were visualised using ultra-violet light (254 nm) and stained using an alkaline potassium permanganate, vanillin, or ninhydrin solution. Column chromatographies were performed under pressure with the stated solvents using Sigma-Aldrich silica gel 60 (70-230 mesh).

 Smith, G. F. *J. Chem. Soc.* **1954**, 3842.	 **p. 212**
 **p. 214**	 **p. 216**
 Tholander, J.; Bergman, J. *Tetrahedron* **1998**, *55*, 6243.	 **p. 218**
 **p. 220**	 **p. 222**
 **p. 224**	 Kaoru, N.; Miyai, T.; Ashish, N.; Shinzaburo, O.; Atsuyoshi, O. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 1179.

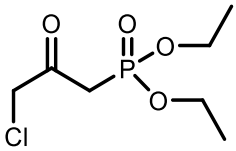
 **p. 226**	 **p. 228**
 **p. 230**	 **p. 232**
 **p. 234**	 Taillier, C.; Hameury, T.; Bellosta, V.; Cossy, J. *Tetrahedron* **2007**, *63*, 4472.
 Taillier, C.; Hameury, T.; Bellosta, V.; Cossy, J. *Tetrahedron* **2007**, *63*, 4472.	 **p. 236**
 **p. 238**	 Bowman, E. R. *J. Chem. Soc. Perkin Trans. I* **1982**, 1897.



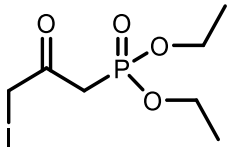
Corbel, B.; Medinger, L.; Haelters, J-P.; Sturtz, G. *Synthesis* **1985**, *11*, 1048.



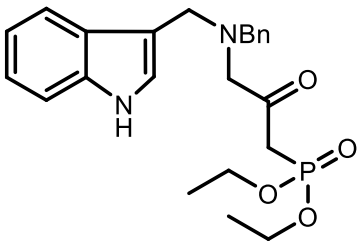
Corbel, B.; Medinger, L.; Haelters, J-P.; Sturtz, G. *Synthesis* **1985**, *11*, 1048.



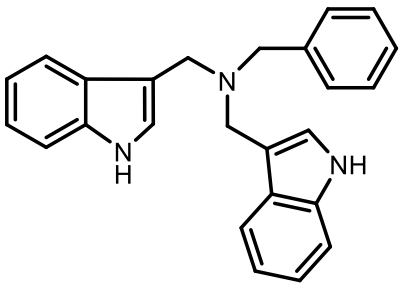
Corbel, B.; Medinger, L.; Haelters, J-P.; Sturtz, G. *Synthesis* **1985**, *11*, 1048.



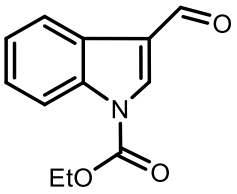
p. 240



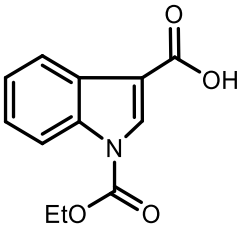
p. 241



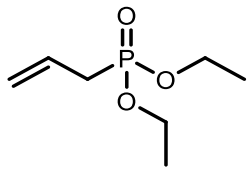
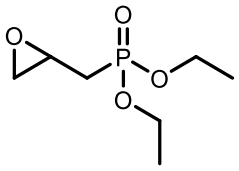
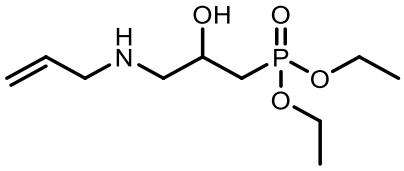
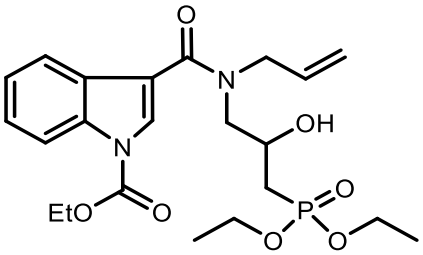
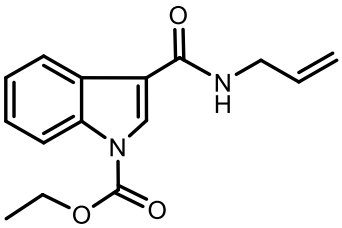
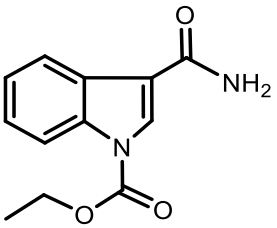
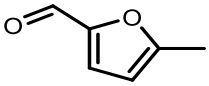
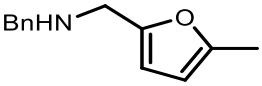
p. 243

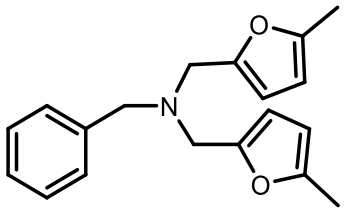


p. 245

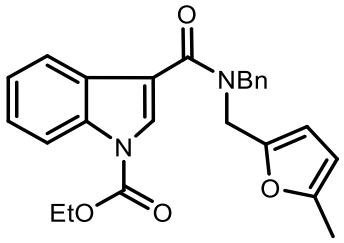


p. 247

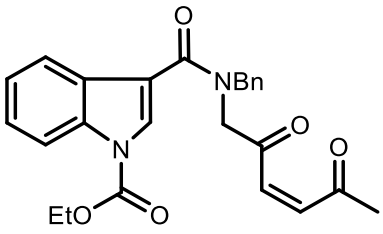
 Platonov, A. Yu.; Sivakov, A. A.; Chistokletov, V. N.; Maiorova, E. D. *Russ. Chem. Bull.* **1999**, *48*, 367.	 **p. 249**
 **p. 251**	 **p. 252**
 **p. 254**	 **p. 255**
 Semple, J. E.; Wang, P. C.; Lysenko, Z.; Jouillé, M. M. *J. Am. Chem. Soc.* **1980**, *102*, 7505.	 Heaney, H.; Papageorgiou, G. *Tetrahedron*, **1996**, *52*, 3473.



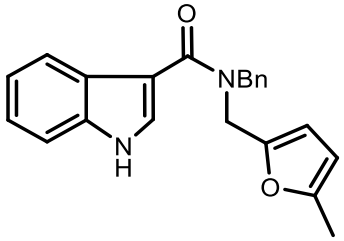
Holdren, R. F.; Hixon, R. M. *J. Am. Chem. Soc*. **1946**, *68*, 1198.



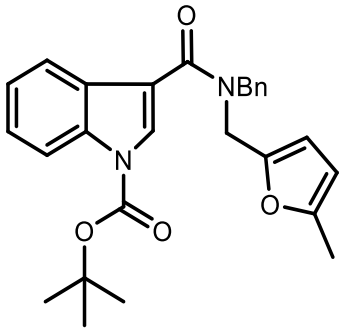
p. 256



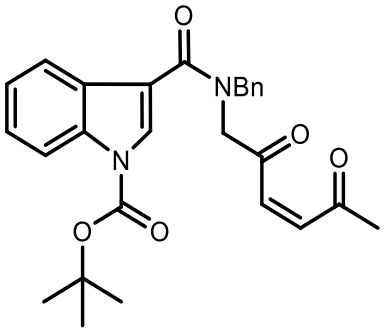
p. 258



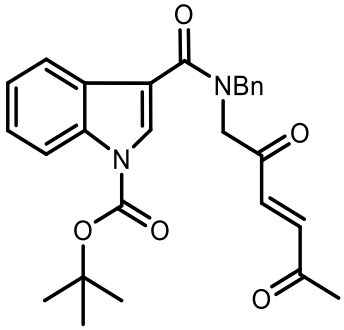
p. 260



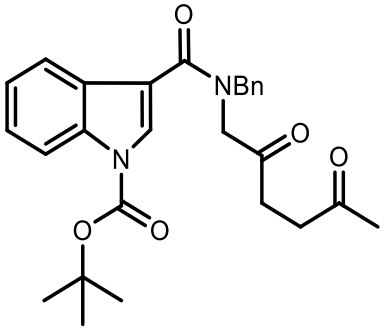
p. 262



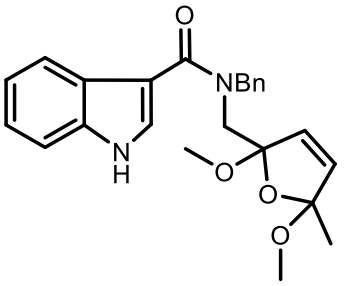
p. 264



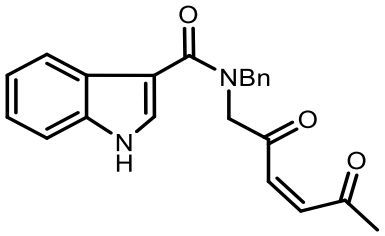
p. 266



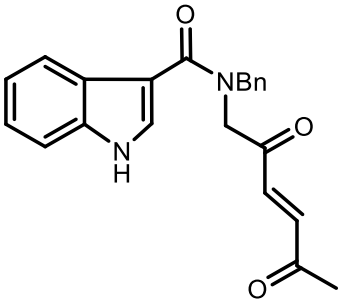
p. 268



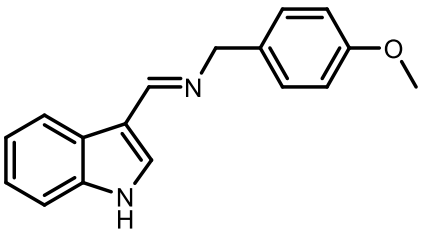
p. 270



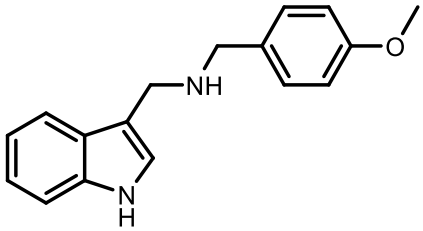
p. 272



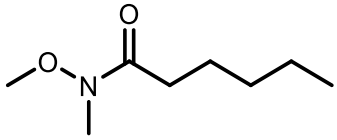
p. 274



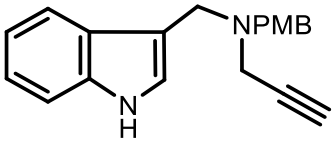
p. 276



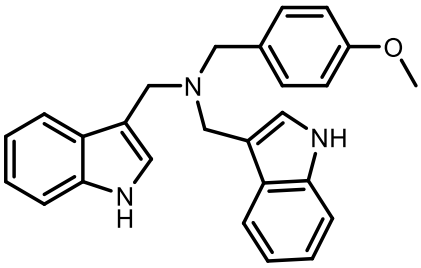
p. 278



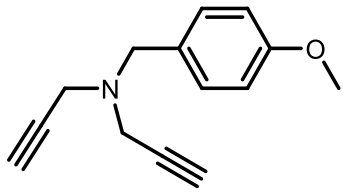
p. 280



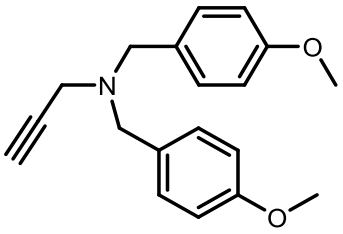
p. 282



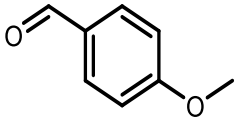
p. 284



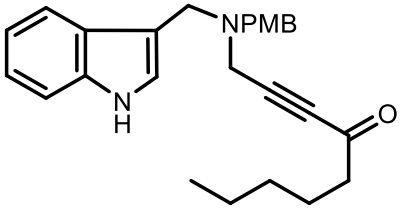
p. 285



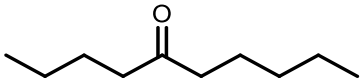
p. 286



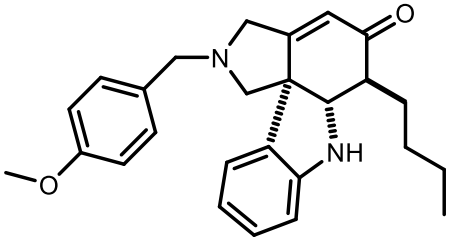
p. 287



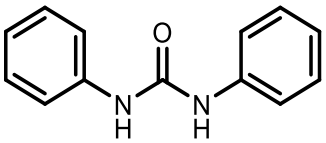
p. 288



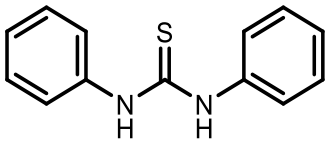
p. 290



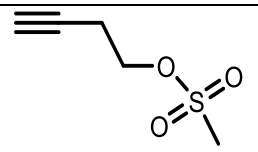
p. 292



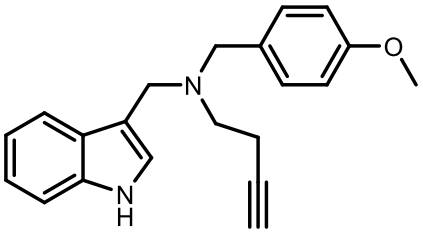
Zhang, M.; Imm, S.; Baehn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3905.



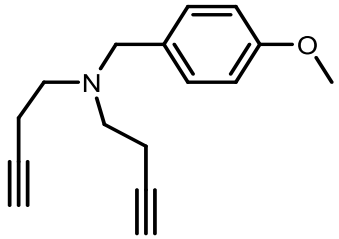
Singh, K.; Sharma, S. *Tetrahedron Lett*. **2017**, *58*, 197.



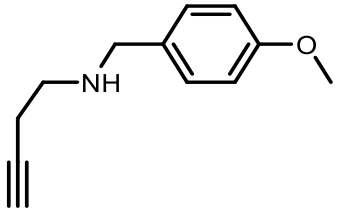
Semioskkin, A. A.; Inyushin, S. G.; Ermanson, L. V.; Petrovskii, P. V.; Lemmen, P.; Bregadze, V. I. *Russ. Chem. Bull.* **1998**, *47*, 1985.



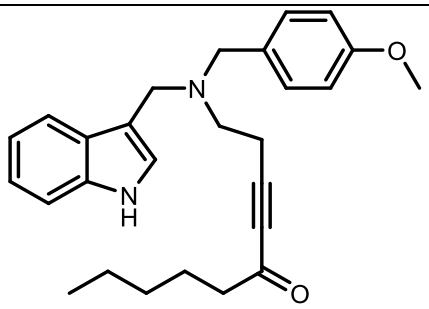
p. 295



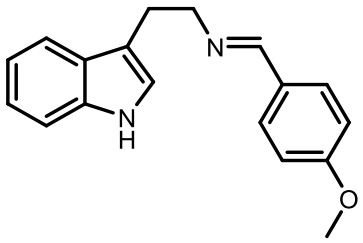
p. 297



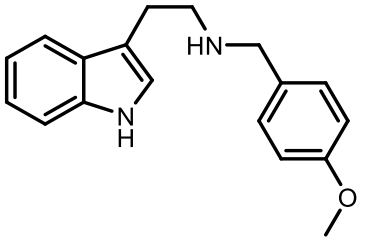
p. 298



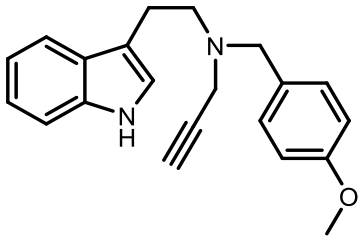
p. 299



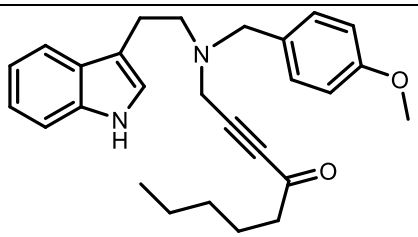
p. 301



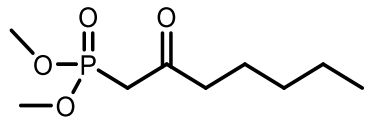
p. 303



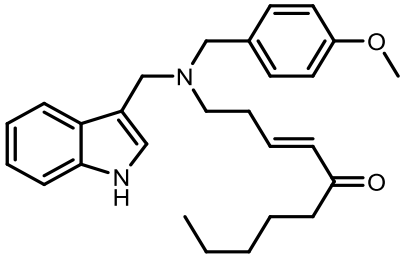
p. 305



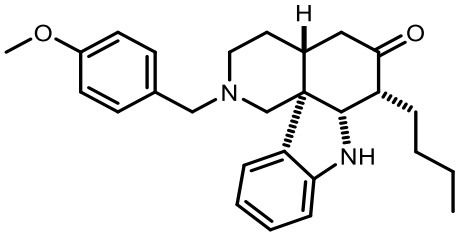
p. 307



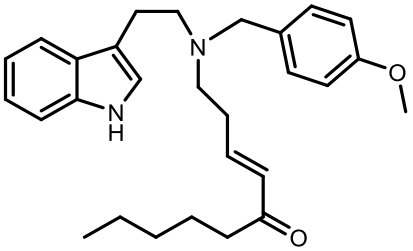
Mathey, F.; Savignac, P. *Tetrahedron* **1978**, *34*, 649.



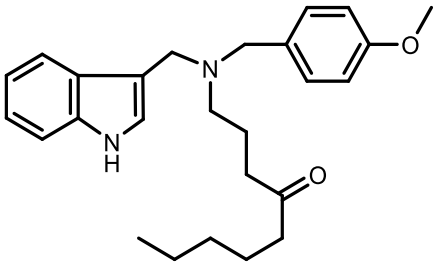
p. 309



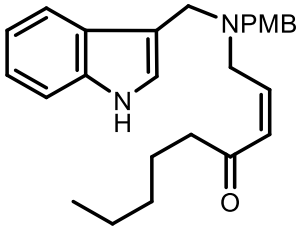
p. 311



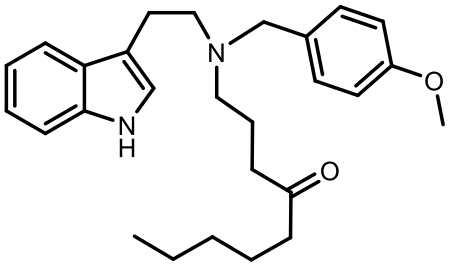
p. 315



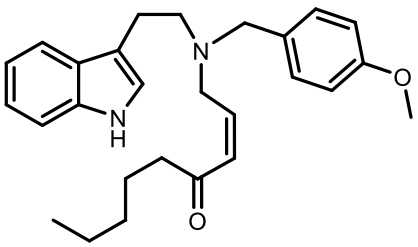
p. 317



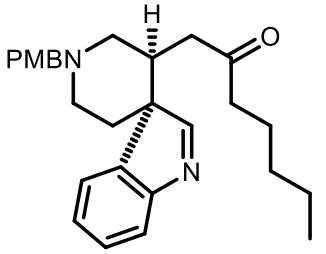
p. 319



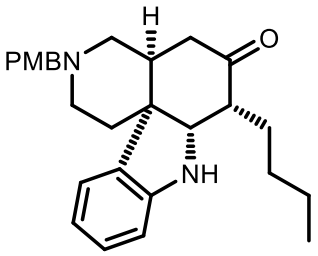
p. 321



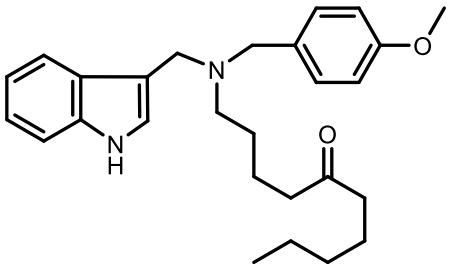
p. 323



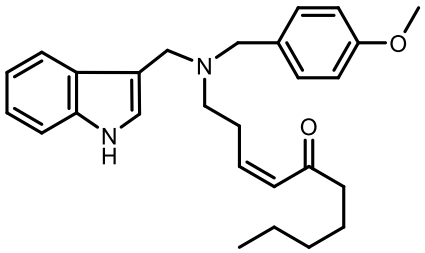
p. 325



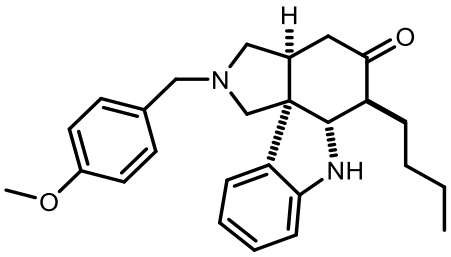
p. 327



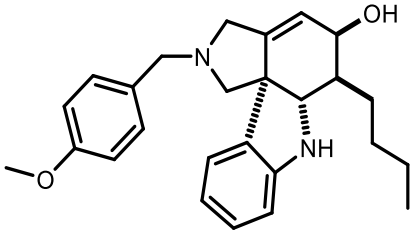
p. 330



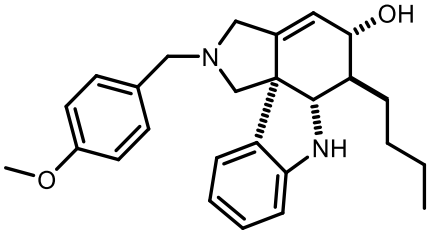
p. 332



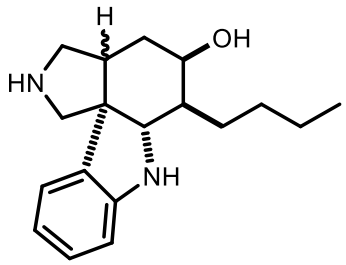
p. 334



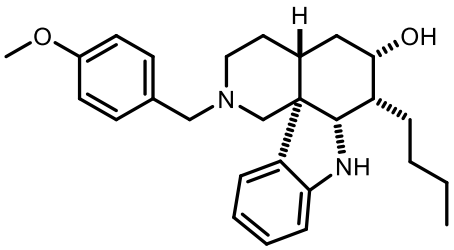
p. 336



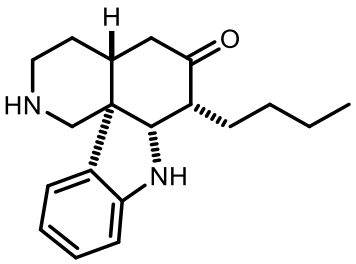
p. 339



p. 343

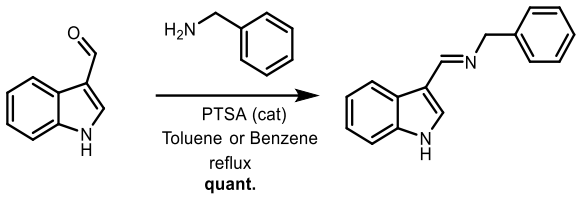


p. 345



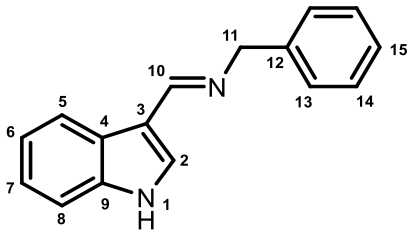
p. 349

N-benzyl-1-(1H-indol-3-yl)methanimine



To as solution of 1H-indole-3-carbaldehyde (40 g, 0.275 mol, 1 eq.) and PTSA (0.24 g, 0.0014 mol, 0.005 eq.) in toluene (350 ml) or benzene (350 ml) was added benzylamine (31 g, 0.289 mol, 1.05 eq., 31.6 ml). The resulting mixture was refluxed with a Dean-Stark apparatus until the correct amount of water (5 ml) was retrieved. The solvent was removed at low pressure to afford a yellow-orange solid; 64.5 g (quantitative).

This solid was directly used without more purification.



CAS: 57506-52-2

Formula: $C_{16}H_{14}N_2$

Molecular weight: 234.30 g/mol

MP: 117-121°C **Litt**[1]**:** 121-122°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (s, 1H, **H1**), 8.57 (s, 1H, **H10**), 8.40 – 8.26 (m, 1H, **H5**), 7.43 – 7.15 (m, 9H, **H2** + **H6** + **H7** + **H8** + **H13** + **H14** + **H15**), 4.82 (s, 2H, **H11**).

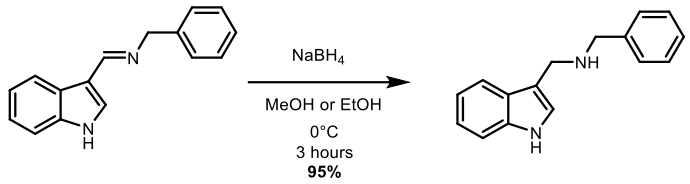
^{13}C NMR (75 MHz, $CDCl_3$) δ 156.62 (**C10**), 140.53 (**C12**), 136.84 (**C9**), 128.74 (**C2**), 128.54 (**C13**/**C14**), 127.95 (**C13**/**C14**), 126.85 (**C15**), 125.60 (**C4**), 123.41 (**C7**), 121.89 (**C5**), 121.51 (**C6**), 115.74 (**C3**), 111.39 (**C8**), 65.58 (**C11**).

[1] Alemany *et al. Bull. Soc. Chem. Fr.* **1975**, 1223.

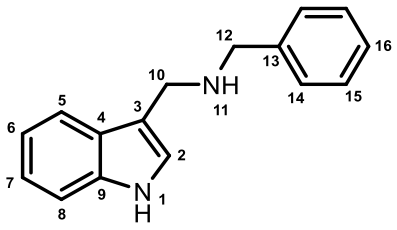
IR (film, cm^{-1}): 3402 (N-H stretching), 3055 (C-H stretching), 3026 (C-H stretching), 2971 (C-H stretching), 2836 (C-H stretching), 1626 (C=N stretching), 1576 (C=C stretching), 1528 (C=C stretching), 1494 (C=C stretching), 1246 (C-N stretching), 733 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of mono-substituted aromatic ring), 695 (C-H bending out of plan of mono-substituted aromatic ring).

The compound was already described in the literature:
Walker, G. N.; Moore, M.A. *J. Org. Chem.*, **1961**, *26*, 432.

N-((1H-indol-3-yl)methyl)-1-phenylmethanamine



N-benzyl-1-(1H-indol-3-yl)methanimine (64.5 g, 0.275 mol, 1 eq.) was dissolved in methanol (300 ml) or ethanol (300 ml) at 0°C. Then $NaBH_4$ (22.9 g, 0.606 mol, 2.2 eq.) was added portionwise and the temperature was kept below 10°C. The mixture was stirred at 0°C for 3 hours then 25-35% aqueous ammonia solution was added (300 ml) and the biphasic mixture was stirred for 2 hours. The solvent was slowly eliminated under vacuum. The resulting aqueous phase was extracted 3 time with dichloromethane, the organic layers were combined and dried over Na_2SO_4. The solvent was eliminated under low pressure providing a yellow solid which can be precipitated with diethyl ether and pentane to a white solid; 61.8 g (95%).



CAS: 57506-64-6

Formula: $C_{16}H_{16}N_2$

Molecular weight: 236.32 g/mol

MP: 82-84°C **Litt**[2]**:** 89-90°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 1H, **H1)**, 7.65 (d, *J* = 7.8 Hz, 1H, **H5**), 7.41 – 7.25 (m, 6H, **H8** + **H14** + **H15** + **H16**), 7.23 – 7.16 (m, 1H, **H7**), 7.16 – 7.06 (m, 2H, **H2** + **H6**), 4.01 (s, 2H, **H10**), 3.88 (s, 2H, **H12**), 1.71 (s, 1H, **H11**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.60 (**C13**), 136.54 (**C9**), 128.53 (**C14**/**C15**), 128.38 (**C14**/**C15**), 127.24 (**C4**), 127.04 (**C16**), 122.66 (**C2**), 122.26 (**C7**),

[2] Bandini, M.; Melloni, A.; Piccinelli, F.; Sinisi, R.; Tommasi, S.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **2006**, *128*, 1424.

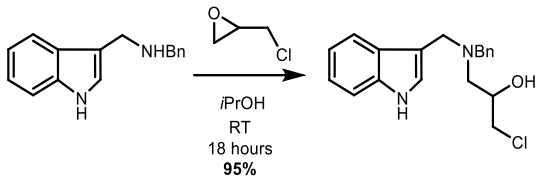
119.65 (**C6**), 119.09 (**C5**), 115.16 (**C3**), 111.30 (**C8**), 53.55 (**C12**), 44.31 (**C10**).

IR (film, cm^{-1}): 3412 (N-H stretching), 3057 (C-H stretching), 3028 (C-H stretching), 2918 (C-H stretching), 2832 (C-H stretching), 1619 (C=C aromatic stretching), 1494 (C=C aromatic stretching), 1453 (CH_2 scissoring), 1232 (C-N stretching), 1090 (C-N stretching), 737 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of mono-substituted aromatic ring), 697 (C-H bending out of plan of mono-substituted aromatic ring).

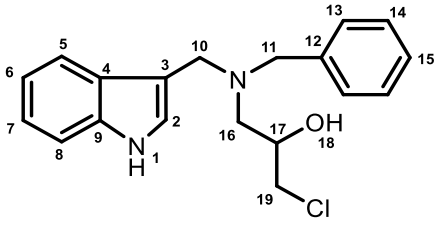
HRMS m/z calculated for $C_{16}H_{17}N_2$ $[M+H]^+$: 237.13863. Found: 237.13812.

The compound was already described in the literature:
Walker, G. N.; Moore, M.A. *J. Org. Chem.*, **1961**, *26*, 432.

1-(((1H-indol-3-yl)methyl)(benzyl)amino)-3-chloropropan-2-ol



N-((1H-indol-3-yl)methyl)-1-phenylmethanamine (4 g, 16.9 mmol, 1 eq.) was dissolved in isopropanol (80 ml), epichlorohydrin (1.7 g, 18.6 mmol, 1.1 eq., 1.46 ml) was added at room temperature. The mixture was stirred at room temperature for 18 hours then the volatiles were removed *in vacuo* to afford a sticky orange oil. This oil was purified by column chromatography using flash silica gel, petroleum ether and ethyl acetate to afford a colourless sticky oil; 5.3 g (95%).



CAS: /

Formula: $C_{19}H_{21}ClN_2O$

Molecular weight: 328.84 g/mol

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.09 (s, 1H, **H1**), 7.58 (dd, *J* = 7.9, 0.6 Hz, 1H, **H5**), 7.39 – 7.26 (m, 6H, **H8** + **H13** + **H14** + **H15**), 7.23 – 7.16 (m, 1H, **H7**), 7.16 – 7.07 (m, 2H, **H2** + **H6**), 3.97 (d, *J* = 13.6 Hz, 1H, **H10**), 3.90 (dq, *J* = 8.0, 5.3 Hz, 1H, **H17**), 3.85 (d, *J* = 13.6 Hz, 1H, **H11**), 3.72 (d, *J* = 13.6 Hz, 1H, **H10'**), 3.54 (d, *J* = 13.3 Hz, 1H, **H11'**), 3.42 (d, *J* = 5.4 Hz, 2H, **H19**), 3.37 (bs, 1H, **H18**), 2.67 (dd, *J* = 12.9, 5.2 Hz, 1H, **H16**), 2.62 (dd, *J* = 12.9, 8.2 Hz, 1H, **H16'**).

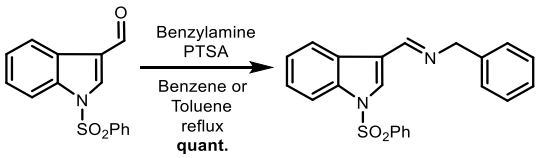
^{13}C NMR (75 MHz, $CDCl_3$) δ 138.77 (**C12**), 136.57 (**C9**), 129.32 (**C13**), 128.60 (**C14**), 127.58 (**C4**), 127.48 (**C15**), 123.98 (**C2**), 122.42 (**C7**), 119.97 (**C6**), 119.24 (**C5**), 112.70 (**C3**), 111.39 (**C8**), 67.83 (**C17**), 59.16 (**C12**), 56.76 (**C16**), 49.93 (**C10**), 47.38 (**C19**).

IR (film, cm^{-1}): 3413 (O-H stretching), 3302 (N-H stretching), 3057 (C-H stretching), 2829 (C-H stretching), 1619 (C=C aromatic stretching), 1493 (C=C aromatic stretching), 1454 (CH_2 scissoring), 1264 (O-H bending in plan), 1237 (C-N stretching), 1091 (C-O stretching), 731 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of mono-substituted aromatic ring), 696 (C-H bending out of plan of mono-substituted aromatic ring).

MS (FTMS +p ESI Full ms) m/z (%): 332.141 (2.6), 331.147 (0.9), 331.138 (12.8), 330.144 (8.8), 329.14 $[M+H]^+$ (40.0), 293.165 (30.0), 259.123 (5.0), 202.080 (32.0), 200.084 (100.0), 164.107 (60.0), 130.065 (10.0), 91.054 (10.0).

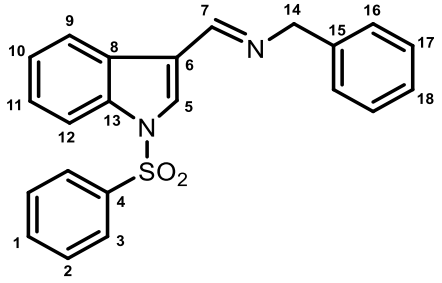
HRMS m/z calculated for $C_{19}H_{22}O_1N_2{}^{35}Cl_1$ $[M+H]^+$: 329.14152. Found: 329.14206.

N-benzyl-1-(1-(phenylsulfonyl)-1H-indol-3-yl)methanimine



To as solution of 1-(phenylsulfonyl)-1H-indole-3-carbaldehyde (20 g, 70 mmol, 1 eq.) and PTSA (0.12 g, 0.7 mmol, 0.01 eq.) in toluene (200 ml) or benzene (200 ml) was added benzylamine (7.88 g, 73.6 mmol, 1.05 eq., 8.04 ml). The resulting mixture was refluxed with a Dean-Stark apparatus until the correct amount of water (1.25 ml) was retrieved. The solvent was removed at low pressure to afford a yellow solid; 26.2 g (quantitative).

This solid was directly used without more purification.



CAS: /

Formula: $C_{22}H_{18}N_2O_2S$

Molecular weight: 374.45 g/mol

MP: 102-105°C **Litt:** /

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.54 (t, *J* = 1.3 Hz, 1H, **H7**), 8.39 (dd, *J* = 7.0, 0.9 Hz, 1H, **H9**), 8.01 – 7.95 (m, 1H, **H12**), 7.95 – 7.83 (m, 3H, **H3** + **H5**), 7.56 (m, 1H, **H1**), 7.50 – 7.41 (m, 2H, **H2**), 7.41 – 7.29 (m, 5H, **H11** + **H16** + **H17**), 7.29 – 7.23 (m, 1H, **H10** + **H18**), 4.83 (d, *J* = 0.8 Hz, 2H, **H14**).

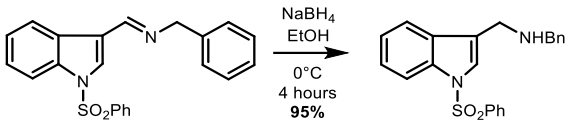
^{13}C NMR (75 MHz, $CDCl_3$) δ 155.05 (**C7**), 139.74 (**C15**), 138.02 (**C4**), 135.68 (**C13**), 134.30 (**C1**), 129.84 (**C5**), 129.57 (**C2**), 128.61 (**C17**), 128.19 (**C8**), 127.95 (**C16**), 127.04 (**C3** + **C18**), 125.86 (**C11**), 124.43 (**C10**), 123.39 (**C9**), 120.92 (**C6**), 113.34 (**C12**), 65.81 (**C14**).

IR (film, cm^{-1}): 3061 (C-H stretching), 3028 (C-H stretching), 2840 (C-H stretching), 1642 (C=N stretching), 1582 (C=C stretching), 1550 (C=C stretching), 1495 (C=C stretching), 1478 (C=C stretching), 1444 (CH_2 scissoring), 1366 (S=O stretching), 1173 (S=O stretching), 1122, 1098 (C-H bending in plan of mono-substituted aromatic ring), 1084 (C-H bending in plan of mono-substituted aromatic ring), 974, 747 (C-H bending out of plan of mono-substituted aromatic ring), 724 (C-H bending out of plan of ortho-disubstituted aromatic ring), 697 (C-H bending out of plan of mono-substituted aromatic ring), 681 (C-H bending out of plan of mono-substituted aromatic ring).

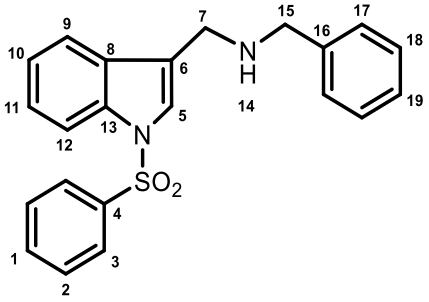
MS (FTMS +p APCI corona Full lock ms) m/z (%): 378.115 (1.1), 377.122 (3.2), 377.112 (4.6), 376.119 (24.4), 375.116 $[M+H]^+$ (100.0), 286.053 (15.0), 234.116 (100.0), 91.055 (100.0).

HRMS m/z calculated for $C_{22}H_{19}O_2N_2{}^{32}S_1$ $[M+H]^+$: 375.11618. Found: 375.11611.

N-benzyl-1-(1-(phenylsulfonyl)-1H-indol-3-yl)methanamine



N-benzyl-1-(1-(phenylsulfonyl)-1H-indol-3-yl)methanimine (25 g, 66.7 mmol, 1 eq.) was dissolved in methanol (300 ml) or ethanol (300 ml) at 0°C. Then $NaBH_4$ (5.56 g, 146.9 mol, 2.2 eq.) was added portionwise and the temperature was kept below 10°C. The mixture was stirred at 0°C for 4 hours then 25-35% aqueous ammonia solution was added (300 ml) and the biphasic mixture was stirred for 6 hours. The solvent was slowly eliminated under vacuum. The resulting aqueous phase was extracted 3 time with dichloromethane, the organic layers were combined and dried over Na_2SO_4. The solvent was eliminated under low pressure providing a yellow solid which can be precipitated with diethyl ether and pentane to a white solid; 23.9 g (95%).



CAS: /

Formula: $C_{22}H_{20}N_2O_2S$

Molecular weight: 376.47 g/mol

MP: 112-115°C **Litt:** /

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.2 Hz, 1H, **H9**), 7.94 – 7.83 (m, 2H, **H3**), 7.56 (d, *J* = 8.1 Hz, 1H, **H12**), 7.54 – 7.48 (m, 2H, **H1** + **H5**), 7.42 (m, 2H, **H2**), 7.37 – 7.28 (m, 8H, **H2** + **H11** + **H17** + **H18** + **H19**), 7.28 – 7.20 (m, 1H, **H10**), 3.90 (s, 2H, **H7**), 3.83 (s, 2H, **H15**), 1.55 (s, 1H, **H14**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 140.17 (**C16**), 138.38 (**C4**), 135.63 (**C13**), 133.87 (**C1**), 130.45 (**C8**), 129.36 (**C2**), 128.60 (**C18**), 128.32 (**C17**), 127.22 (**C19**),

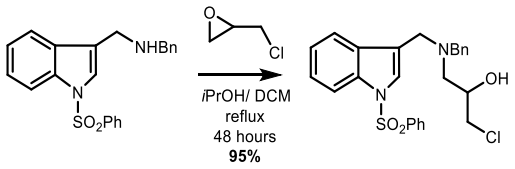
126.88 (**C3**), 125.01 (**C11**), 123.79 (**C5**), 123.37 (**C10**), 121.95 (**C6**), 119.99 (**C12**), 113.87 (**C9**), 53.53 (**C15**), 43.97 (**C7**).

IR (film, cm^{-1}): 3061 (C-H stretching), 3027 (C-H stretching), 2826 (C-H stretching), 1604 (C=C stretching), 1494 (C=C aromatic stretching), 1445 (CH_2 scissoring), 1364 (S=O stretching), 1172 (S=O stretching), 1118, 1091 (C-H bending in plan of mono-substituted aromatic ring), 973, 743 (C-H bending out of plan of mono-substituted aromatic ring), 722 (C-H bending out of plan of ortho-disubstituted aromatic ring), 698 (C-H bending out of plan of mono-substituted aromatic ring), 684 (C-H bending out of plan of mono-substituted aromatic ring).

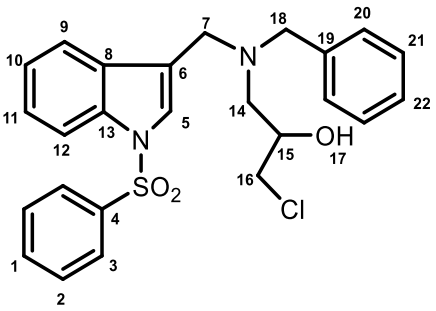
MS (FTMS +p APCI corona Full lock ms) m/z (%): 380.131 (0.3), 379.138 (1.0), 379,127 (1.4), 378.135 (7.3), 377.131 (30.0), 270.058 (100).

HRMS m/z calculated for $C_{22}H_{21}O_2N_2{}^{32}S_1$ $[M+H]^+$: 377.13183. Found: 377.13176.

1-(benzyl((1-(phenylsulfonyl)-1H-indol-3-yl)methyl)amino)-3-chloropropan-2-ol



N-benzyl-1-(1-(phenylsulfonyl)-1H-indol-3-yl)methanamine (3 g, 7.9 mmol, 1 eq.) was dissolved in isopropanol (40 ml) and dichloromethane (20 ml), then epichlorohydrin (2.2 g, 23.9 mmol, 3 eq., 1.87 ml) was added at room temperature. The mixture was stirred at reflux for 48 hours then the volatiles were removed *in vacuo* to afford the desired product as a sticky orange oil; 3.55 g (95%).



CAS: /

Formula: $C_{25}H_{25}ClN_2O_3S$

Molecular weight: 468.99 g/mol

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.3 Hz, 1H, **H9**), 7.88 – 7.79 (m, 2H, **H3**), 7.55 – 7.46 (m, 2H, **H1** + **H5**), 7.46 – 7.36 (m, 3H, **H12** + **H2**), 7.36 – 7.17 (m, 7H, **H11** + **H10** + **H20** + **H21** + **H22**), 3.93 – 3.72 (m, 3H, **H7** + **H15** + **H18**), 3.61 (d, *J* = 13.7 Hz, 1H, **H7'**), 3.50 (d, *J* = 13.2 Hz, 1H, **H18'**), 3.41 – 3.29 (m, 2H, **H16**), 2.99 (bs, 1H, **H17**), 2.68 – 2.50 (m, 2H, **H14**).

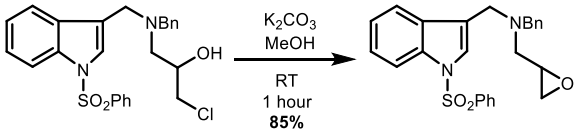
^{13}C NMR (75 MHz, $CDCl_3$) δ 138.12 (**C19**), 137.93 (**C4**), 135.53 (**C13**), 133.84 (**C1**), 130.47 (**C8**), 129.25 (**C20**), 129.19 (**C2**), 128.53 (**C21**), 127.52 (**C22**), 126.62 (**C3**), 125.23 (**C5**), 125.08 (**C11**), 123.52 (**C10**), 119.98 (**C12**), 119.92 (**C6**), 113.81 (**C9**), 67.84 (**C15**), 59.20 (**C18**), 56.79 (**H14**), 49.48 (**C7**), 47.38 (**C16**).

IR (film, cm^{-1}): 3425 (O-H stretching), 3062 (C-H stretching), 3028 (C-H stretching), 2830 (C-H stretching), 1605 (C=C aromatic stretching), 1494 (C=C aromatic stretching), 1446 (CH_2 scissoring), 1366 (C-N stretching of tertiary amine + S=O stretching), 1279 (O-H bending in plan), 1173 (S=O stretching), 1119 (C-O stretching), 977, 908, 745 (C-H bending out of plan of mono-substituted aromatic ring), 724 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of mono-substituted aromatic ring), 699 (C-H bending out of plan of mono-substituted aromatic ring), 684 (C-H bending out of plan of mono-substituted aromatic ring).

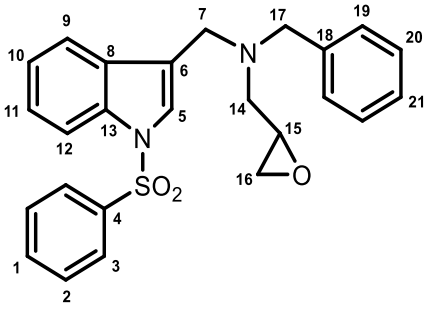
MS (FTMS +p APCI corona Full lock ms) m/z (%): 473.136 (1.7), 473.128 (1.7), 472.134 (10.3), 471.131 (36.9), 470.137 (28.1), 469.134 $[M+H]^+$ (100.0), 433.157 (20.0), 375.115 (12.2), 286.052 (10.0), 270.057 (70.0).

HRMS m/z calculated for $C_{25}H_{26}O_3N_2{}^{35}Cl_1{}^{32}S_1$ $[M+H]^+$: 469.13472. Found: 469.13434.

N-benzyl-1-(oxiran-2-yl)-N-((1-(phenylsulfonyl)-1H-indol-3-yl)methyl)methanamine



1-(benzyl((1-(phenylsulfonyl)-1H-indol-3-yl)methyl)amino)-3-chloropropan-2-ol (3.55 g, 7.5 mmol, 1 eq.) was dissolved in methanol (80 ml) at room temperature then potassium carbonate (5.23 g, 37.8 mmol, 5 eq.) was added at once. The resulting mixture was stirred at room temperature for 1 hour. Water and dichloromethane were added, and the solution extracted with dichloromethane, the organic phases were combined and dried over magnesium sulfate. The volatiles were removed *in vacuo* to afford the desired product as a colourless oil; 2.78 g (85%).



CAS: /

Formula: $C_{25}H_{24}N_2O_3S$

Molecular weight: 432.53 g/mol

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.2 Hz, 1H, **H9**), 7.87 – 7.80 (m, 2H, **H3**), 7.65 (d, *J* = 7.8 Hz, 1H, **H12**), 7.52 (s, 1H, **H5**), 7.52 – 7.44 (m, 1H, **H1**), 7.41 – 7.33 (m, 3H, **H2** + **H10**), 7.33 – 7.19 (m, 6H, **H11** + **H19** + **H20** + **H21**), 3.89 (d, *J* = 13.9 Hz, 1H, **H7**), 3.79 (d, *J* = 13.5 Hz, 1H, **H17**), 3.67 (d, *J* = 14.2 Hz, 1H, **H7**), 3.51 (d, *J* = 13.5 Hz, 1H, **H17'**), 3.07 (td, *J* = 6.7, 3.2 Hz, 1H, **H15**), 2.81 (dd, *J* = 13.8, 3.3 Hz, 1H, **H14**), 2.69 – 2.62 (m, 1H, **H16**), 2.38 (dd, *J* = 5.6, 3.4 Hz, 1H, **H16'**), 2.36 (dd, *J* = 14.5, 5.9 Hz, 1H, **H14'**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 139.06 (**C18**), 138.10 (**C4**), 135.68 (**C13**), 133.80 (**C1**), 130.86 (**C8**), 129.24 (**C2**), 129.00 (**C19**), 128.35 (**C20**), 127.17 (**C21**),

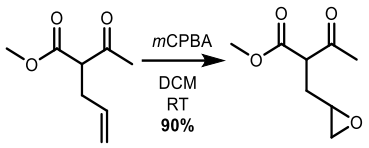
126.70 (**C3**), 124.95 (**C5** + **C10**), 123.33 (**C11**), 120.95 (**C6**), 120.74 (**C12**), 113.75 (**C9**), 59.17 (**C17**), 55.96 (**C14**), 51.10 (**C15**), 49.84 (**C7**), 44.84 (**C16**).

IR (film, cm^{-1}): 3083 (C-H stretching), 3061 (C-H stretching), 3028 (C-H stretching), 2922 (C-H stretching), 2803 (C-H stretching), 1604 (C=C aromatic stretching), 1494 (C=C aromatic stretching), 1446 (CH_2 scissoring), 1368 (S=O stretching + C-N stretching of tertiary amine), 1174 (S=O stretching), 1095 (C-O stretching), 978, 746 (C-H bending out of plan of mono-substituted aromatic ring), 724 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of mono-substituted aromatic ring), 699 (C-H bending out of plan of mono-substituted aromatic ring), 685 (C-H bending out of plan of mono-substituted aromatic ring).

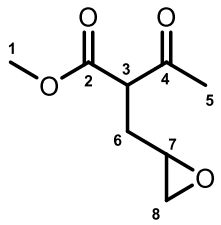
MS (FTMS +p ESI Full ms) m/z (%): 455.142 $[M+Na]^+$ (15.0), 436.157 (1.3), 435.163 (4.4), 435.154 (4.8), 434.161 (28.0), 433.158 $[M+H]^+$ (100.0), 369.234 (5.0), 314.213 (30.0), 270.059 (42.5), 244. 131 (10), 242.131 (30), 206.155 (16.0).

HRMS m/z calculated for $C_{25}H_{25}O_3N_2{}^{32}S_1$ $[M+H]^+$: 433.15804. Found: 433.16059.

methyl 2-(oxiran-2-ylmethyl)-3-oxobutanoate



To a solution of methyl 2-acetylpent-4-enoate (6.06 g, 38.8 mmol, 1 eq., 6 ml) in dichloromethane (120 ml) was added dry *meta*-chloroperoxybenzoic acid (7.7 g, 44.4 mmol, 1.15 eq.) at room temperature. The mixture was stirred at this temperature until completion by TLC approximately 3 days and quenched by addition of isoprene. The resulting mixture was washed with a saturated solution of sodium bicarbonate in water, and the water phase was extracted with dichloromethane. The organic layers were combined and dried over sodium sulfate to afford a colourless oil; 6 g (90 %)



CAS: /

Formula: $C_8H_{12}O_4$

Molecular weight: 172.18 g/mol

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.77 (d, *J* = 4.9 Hz, 3H, **H1** + **H1'**), 3.74 – 3.65 (m, 1H, **H3**), 3.04 – 2.91 (m, 1H, **H7**), 2.78 (dd, *J* = 8.8, 4.7 Hz, 1H, **H8**), 2.51 (dt, *J* = 5.0, 2.6 Hz, 1H, **H8'**), 2.40 – 2.22 (m, 4H, **H5** + **H6**), 1.95 – 1.76 (m, 1H, **H6'**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 202.21 (**C4**), 202.17 (**C4'**), 169.79 (**C2**), 169.70 (**C2'**), 56.36 (**C3**), 55.90 (**C3'**), 52.81 (**C1**), 52.76 (**C1'**), 50.05 (**C7**), 49.94 (**C7'**), 47.57 (**C8**), 47.35 (**C8'**), 31.00 (**C6**), 30.73 (**C6'**), 29.67 (**C5**), 29.22 (**C5'**).

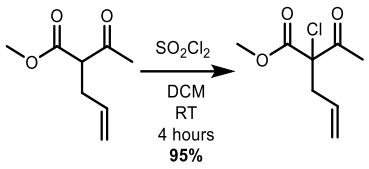
IR (film, cm^{-1}): 3001 (C-H stretching), 2956 (C-H stretching), 2930 (C-H stretching), 1738 (C=O stretching from saturated acyclic ester), 1714 (C=O stretching from saturated acyclic ketone), 1435 (CH_3 asymmetric

deformation), 1359 (CH in plan bending), 1231 (C-O stretching), 1195 (C-O stretching), 1148 (C-O stretching), 874.

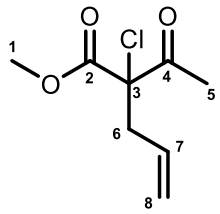
(MS (FTMS +p APCI corona Full ms) m/z (%): 175.085 (0.8), 174.084 (8.8), 173.080 (100.0), 155.070 (32.01), 141.054 (17.4), 113.0599 (12.6), 99.044 (30.5).

HRMS m/z calculated for $C_8H_{13}O_4$ $[M+H]^+$: 173.08084. Found: 173.08084.

methyl 2-acetyl-2-chloropent-4-enoate



To a solution of methyl 2-acetylpent-4-enoate (1.01 g, 6.5 mmol, 1 eq., 1 ml) in dichloromethane (12 ml) at room temperature was added dropwise sulfuryl chloride (0.96 g, 7.1 mmol, 1.1 eq., 0.58 ml) and the mixture was stirred for 4 hours at room temperature. The mixture was purred in water (16 ml) and extracted with dichloromethane. The organic phases were combined, dried over sodium sulfate and the volatiles were removed without an excessive vacuum to afford the desired product as a colourless oil; 1.18 g (95%).



CAS: /

Formula: $C_8H_{11}ClO_3$

Molecular weight: 190.62 g/mol

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.79 (dddd, *J* = 16.7, 14.2, 10.0, 5.2 Hz, 1H, **H7**), 5.24 – 5.13 (m, 2H, **H8**), 3.82 (s, 3H, **H1**), 2.91 (qdt, *J* = 14.6, 7.0, 1.1 Hz, 2H, **H6**), 2.35 (s, 3H, **H5**).

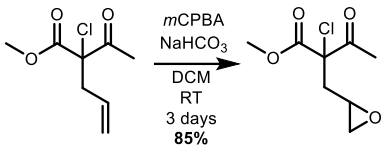
^{13}C NMR (75 MHz, $CDCl_3$) δ 198.22 (**C4**), 167.65 (**C2**), 130.76 (**C7**), 120.64 (**C8**), 74.55 (**C3**), 53.82 (**C1**), 41.25 (**C6**), 26.16 (**C5**).

IR (film, cm^{-1}): 3082 (C-H stretching), 3012 (C-H stretching), 2985 (C-H stretching), 2957 (C-H stretching), 1727 (C=O stretching), 1643 (C=C stretching from mono-alkylated alkene), 1262, 1236 (C-O stretching), 1216, 1178 (C-O stretching), 1130 (C-C stretching), 993 (C-H bending out of plan of mono-substituted alkene), 927 (C-H bending out of plan of mono-substituted alkene).

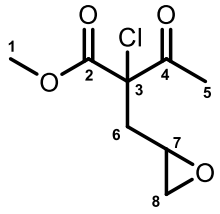
MS (FTMS +p ESI Full ms) m/z (%): 219.099 (100.0), 213.029 (60.1), 197.117 (22.9), 173.078 (4.2), 151.005 (22.1), 77.022 (5.0).

HRMS m/z calculated for $C_8H_{11}O_3{}^{35}Cl_1{}^{23}Na_1$ $[M+Na]^+$: 213.02889. Found: 213.02939

methyl 2-chloro-2-(oxiran-2-ylmethyl)-3-oxobutanoate



To a solution of methyl 2-acetyl-2-chloropent-4-enoate (3.0 g, 15.7 mmol, 1 eq.) and sodium bicarbonate [3] (2.0 g, 23.6 mmol, 1.5 eq.) in dichloromethane (60 ml) was added dry *meta*-chloroperoxybenzoic acid (4.65 g, 18.9 mmol, 1.2 eq.) at room temperature. The mixture was stirred at this temperature until completion by TLC and quenched by addition of isoprene. The resulting mixture was washed with a saturated solution of sodium bicarbonate in water, and the water phase was extracted with dichloromethane. The organic layers were combined and dried over sodium sulfate to afford a colourless oil; 2.76 g (85 %).[4]



CAS: /

Formula: $C_8H_{11}ClO_4$

Molecular weight: 206.62 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H, **H1**), 3.85 (s, 3H, **H1'**), 3.16 (qdd, *J* = 5.8, 4.1, 2.6 Hz, 2H, **H7** + **H7'**), 2.80 (ddd, *J* = 6.7, 4.9, 4.1 Hz, 2H, **H8**), 2.57 – 2.44 (m, 4H, **H6** + **H8'**), 2.42 (s, 3H, **H5**), 2.36 (s, 3H, **H5'**), 2.33 – 2.23 (m, 2H, **H6'**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.57 (**C4**), 197.18 (**C4'**), 167.76 (**C2**), 167.61 (**C2'**), 72.99 (**C3**), 72.63 (**C3'**), 54.17 (**C1**), 54.06 (**C1'**), 48.09 (**C7**), 47.96

[3] Tip: the use of sodium bicarbonate in the reaction is not mandatory if methyl 2-acetyl-2-chloropent-4-enoate was washed with a saturated aqueous solution of sodium bicarbonate. The presence of HCl in the reaction increase the quantity of bicyclic side product and decrease the yield.

[4] By NMR two diastereoisomers could be observed with a 1:1 ratio.

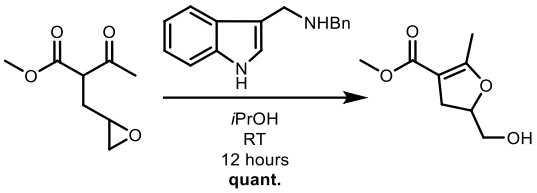
(**C7'**), 47.09 (**C8**), 46.94 (**C8'**), 40.39 (**C6**), 40.14 (**C6'**), 26.18 (**C5**), 25.28 (**C5'**).

IR (film, cm^{-1}): 3066 (C-H stretching), 3006 (C-H stretching), 2957 (C-H stretching), 2929 (C-H stretching), 1726 (C=O stretching), 1434 (CH_3 asymmetric deformation), 1237 (C-O stretching), 738 (C-Cl stretching).

HRMS m/z calculated for $C_8H_{11}{}^{35}Cl_1O_4{}^{23}Na_1$ $[M+Na]^+$: 229.0243. Found: 229.0235.

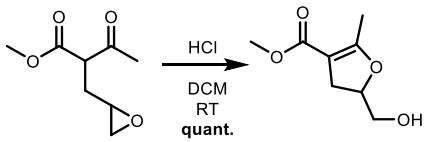
methyl 5-(hydroxymethyl)-2-methyl-4,5-dihydrofuran-3-carboxylate

Methode A:



To a solution of N-((1H-indol-3-yl)methyl)-1-phenylmethanamine (0.92 g, 3.9 mmol, 0.6 eq.) in isopropanol (20 ml) at room temperature was added methyl 2-(oxiran-2-ylmethyl)-3-oxobutanoate (1.11 g, 6.5 mmol, 1 eq.). The mixture was stirred at room temperature for 12 hours then the solvent was evaporated under vacuum to provide a yellow oil. This oil was purified by column chromatography using flash silica gel, petroleum ether and ethyl acetate to afford a colourless oil; 1.11 g (quantitative).

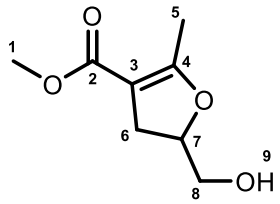
Methode B:



To a solution of methyl 2-(oxiran-2-ylmethyl)-3-oxobutanoate (1.11 g, 6.5 mmol, 1 eq.) in dichloromethane (20 ml) at room temperature was added a solution of dry HCl (0.01 eq.) in dichloromethane (1 ml) then the mixture was stirred at room temperature for 12 hours. The volatiles were removed *in vacuo* to obtain a colourless oil; 1.11 g (quantitative).

CAS: /

Formula: $C_8H_{12}O_4$



Molecular weight: 172.18 g/mol

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.75 (dddd, *J* = 10.4, 7.8, 6.5, 3.7 Hz, 1H, **H7**), 3.76 – 3.62 (m, 5H, **H1** + **H8**), 2.93 (ddq, *J* = 13.7, 10.6, 1.5 Hz, 1H, **H6**), 2.62 (ddq, *J* = 14.4, 7.8, 1.6 Hz, 1H, **H6'**), 2.20 (t, *J* = 1.6 Hz, 3H, **H5**), 1.99 (bs, 1H, **H9**).

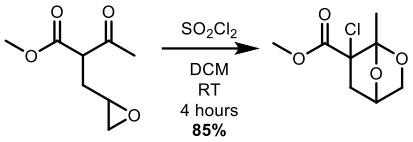
^{13}C NMR (75 MHz, $CDCl_3$) δ 167.90 (**C4**), 166.56 (**C2**), 102.09 (**C3**), 82.57 (**C7**), 65.10 (**C8**), 51.04 (**C1**), 31.37 (**C6**), 14.18 (**C5**).

IR (film, cm^{-1}): 3410 (O-H stretching), 2951 (C-H stretching), 2871 (C-H stretching), 1682 (C=C stretching of tetra-substituted alkene), 1637 (C=O stretching of enol-ester), 1438 (CH_3 asymmetric deformation), 1385 (CH_3 symmetric deformation), 1225 (C-O stretching), 1088 (C-O stretching).

HRMS m/z calculated for $C_8H_{13}O_4$ $[M+H]^+$: 173.08084. Found: 173.08080.

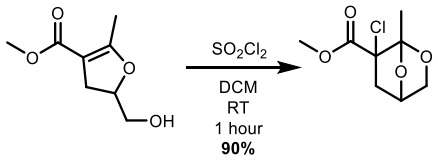
methyl 6-chloro-1-methyl-2,7-dioxabicyclo[2.2.1]heptane-6-carboxylate[5]

Methode A:



To a solution of methyl 2-chloro-2-(oxiran-2-ylmethyl)-3-oxobutanoate (0.5 g, 2.9 mmol, 1 eq.) in dichloromethane (10 ml) was added drop wisely sulfuryl chloride (0.4 g, 3 mmol, 1.05 eq. 0.25 ml) at room temperature, the mixture was stirred at room temperature for 4 hours then purred on a saturated aqueous solution of sodium bicarbonate and dichloromethane. The resulting biphasic mixture was vigorously shake and extracted with dichloromethane, dried over sodium sulfate, then the volatiles were removed *in vacuo* to afford a colourless oil; 0.51 g (85%).

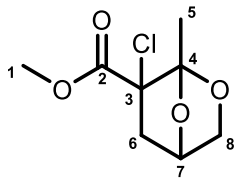
Methode B:



To a solution of methyl 5-(hydroxymethyl)-2-methyl-4,5-dihydrofuran-3-carboxylate (0.5 g, 2.9 mmol, 1 eq.) in dichloromethane (10 ml) was added drop wisely sulfuryl chloride (0.4 g, 3 mmol, 1.05 eq. 0.25 ml) at room temperature, the mixture was stirred at room temperature for 1

[5] Tip: This product can appear as crystalline drops, the small proportion of diastereoisomer probably prevent a proper crystallisation. This diastereoisomer can be observed by ^{13}C NMR as small picks next the major product.

hour then purred on a saturated aqueous solution of sodium bicarbonate and dichloromethane. The resulting biphasic mixture was vigorously shake and extracted with dichloromethane, dried over sodium sulfate, then the volatiles were removed *in vacuo* to afford a colourless oil; 0.54 g (90%).



CAS: /

Formula: $C_8H_{11}ClO_4$

Molecular weight: 206.62 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.83 (dd, *J* = 5.4, 3.1 Hz, 1H, **H7**), 3.82 (s, 3H, **H1**), 3.66 (ddd, *J* = 6.5, 3.1, 2.3 Hz, 1H, **H8**), 3.63 (t, *J* = 6.6 Hz, 1H, **H8'**), 3.13 (d, *J* = 13.5 Hz, 1H, **H6**), 2.35 (ddd, *J* = 13.7, 5.5, 2.2 Hz, 1H, **H6'**), 1.85 (s, 3H, **H5**).

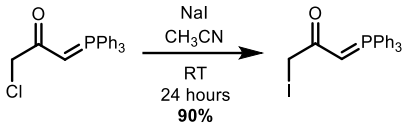
^{13}C NMR (100 MHz, $CDCl_3$) δ 168.71 (**C2**), 109.61 (**C4**), 76.57 (**C7**), 71.69 (**C3**), 70.13 (**C8**), 53.45 (**C1**), 44.83 (**C6**), 14.90 (**C5**).

IR (film, cm^{-1}): 3007 (C-H stretching), 2955 (C-H stretching), 2899 (C-H stretching), 1739 (C=O stretching of acyclic saturated ester), 1436 (CH_3 asymmetric deformation), 1393, 1299 (C-O stretching), 1265 (C-O stretching), 1060 (C-O stretching), 964 (C-O stretching).

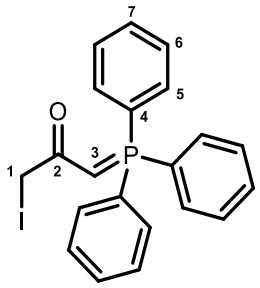
MS (FTMS +p ESI Full ms) m/z (%): 326.115 (100.0), 319.144 (40.1), 207.041 (10.1), 198.127 (40.0).

HRMS m/z calculated for $C_8H_{12}O_4{}^{35}Cl_1$ $[M+H]^+$: 207.04186. Found: 207.04195

1-iodo-3-(triphenyl-l5-phosphaneylidene)propan-2-one



To a solution of 1-chloro-3-(triphenyl-l5-phosphaneylidene)propan-2-one (3 g, 8.5 mmol, 1 eq.) in anhydrous acetonitrile (40 ml) was added sodium iodide (3.2 g, 21.3 mmol, 2.5 eq.). The mixture was stirred for 24 hours at room temperature then solvent was removed *in vacuo* and the resulting solid was dissolved in dichloromethane and water. The aqueous phase was extracted with dichloromethane, the organic phases were combined and dried over sodium sulfate. All the volatiles were removed to afford the desired iodophosphorane as a brown solid; 3.4 g (90%)



CAS: /

Formula: C21H18IOP

Molecular weight: 444.25 g/mol

MP: decomp > 110°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72 – 7.61 (m, 6H, **H5**), 7.61 – 7.53 (m, 3H, **H7**), 7.53 – 7.43 (m, 6H, **H6**), 4.12 (d, *J* = 24.2 Hz, 1H, **H3**), 3.85 (d, *J* = 2.3 Hz, 2H, **H1**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 185.51 (d, *J* = 5.6 Hz, **C2**), 133.12 (d, *J* = 10.2 Hz, **C5**), 132.46 (**C7**), 129.07 (d, *J* = 12.4 Hz, **C6**), 126.19 (d, *J* = 90.5 Hz, **C4**), 51.91 (d, *J* = 104.9 Hz, **C3**), 9.76 (d, *J* = 18.2 Hz, **C1**).

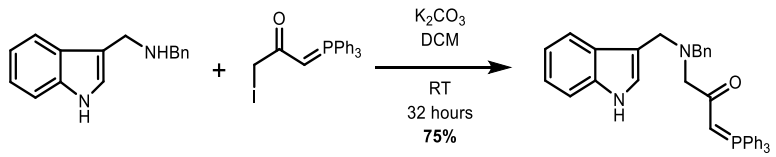
IR (film, cm^{-1}): 3053 (C-H stretching), 1625 (C=O stretching/ C=C stretching), 1574 (C=C aromatic stretching), 1534 (C=C aromatic stretching), 1435, 1380, 1102, 714 (C-H bending out of plan of mono-

substituted aromatic ring), 686 (C-H bending out of plan of mono-substituted aromatic ring), 495 (C-I stretching).

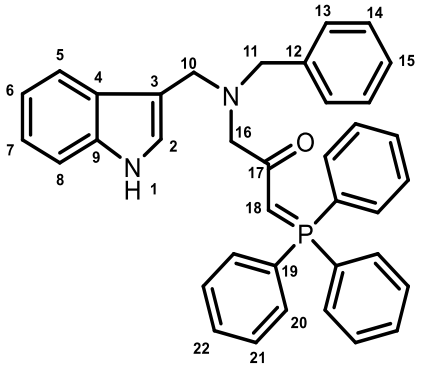
MS (FTMS +p ESI Full ms2) m/z (%): 445.020 $[M+H]^+$ (100.0), 318.116 (30.0), 303.092 (3.0), 275.097 (3.0), 275.097 (9.0), 227.061 (12.0), 203.061 (42.5), 185.051 (1.0).

HRMS m/z calculated for $C_{21}H_{19}O_1{}^{127}I_1P_1$ $[M+H]^+$: 445.02127. Found: 445.02146.

1-(((1H-indol-3-yl)methyl)(benzyl)amino)-3-(triphenyl-l5-phosphaneylidene)propan-2-one



To a solution of N-((1H-indol-3-yl)methyl)-1-phenylmethanamine (1.59 g, 6.7 mmol, 1 eq.) and potassium carbonate (1.12 g, 8.1 mmol, 1.2 eq.) in dichloromethane (30 ml) at room temperature was added 1-iodo-3-(triphenyl-l5-phosphaneylidene)propan-2-one (15 ml) in dichloromethane and the mixture was stirred at room temperature for 32 hours then extracted with dichloromethane and water. The organic phases were combined and dried over sodium sulfate, the volatiles were removed *in vacuo* to afford a brown solid. This solid was dropped in diethyl ether and stirred overnight to obtain the desired product as a yellow solid; 2.8 g (75%)



CAS: /

Formula: $C_{37}H_{33}N_2OP$

Molecular weight: 552.65 g/mol

MP: decomp >130°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 – 7.30 (m, 16H, **H5** + **H20** + **H21** + **H22**), 7.29 – 7.13 (m, 6H, **H8** + **H13** + **H14** + **H15**), 7.10 – 7.01 (m, 1H, **H7**), 6.93 (d, *J* = 2.1 Hz, 1H, **H2**), 6.88 – 6.79 (m, 1H, **H6**), 3.90 (s, 2H, **H10**), 3.78 (s, 2H, **H11**), 3.77 (d, *J* = 23.1 Hz, 1H, **H18**), 3.23 (s, 2H, **H16**).

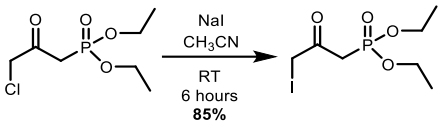
^{13}C NMR (75 MHz, $CDCl_3$) δ 191.33 (d, *J* = 2.3 Hz, **C17**), 139.66 (**C12**), 136.68 (**C9**), 136.63 (**C9**), 133.10 (d, *J* = 10.2 Hz, **C20**), 132.13 (d, *J* = 9.7 Hz, **C22**), 129.23 (**C13**), 128.91 (d, *J* = 12.3 Hz, **C21**), 128.19 (**C14**), 126.85 (**C15**), 126.82 (d, *J* = 90.6 Hz, **C19**), 124.77 (**C2**), 124.23 (**C2'**), 121.40 (**C7**), 121.27 (**C7'**), 119.71 (**C5**), 119.61 (**C5'**), 118.82 (**C6**), 118.73 (**C6'**), 112.05 (**C3**), 111.53 (**C8**), 111.39 (**C8'**), 62.69 (d, *J* = 13.2 Hz, **C16**), 59.03 (**C11**), 51.96 (d, *J* = 111.6 Hz, **C18**), 50.27 (**C10**).

IR (film, cm^{-1}): 3174 (N-H stretching), 3055 (C-H stretching), 2915 (C-H stretching), 2782 (C-H stretching), 1518 (C=C stretching), 1491 (C=C stretching), 1482 (CH_2 scissoring), 1436, 1107, 738 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of mono-substituted aromatic ring), 718 (C-H bending out of plan of mono-substituted aromatic ring), 692 (C-H bending out of plan of mono-substituted aromatic ring).

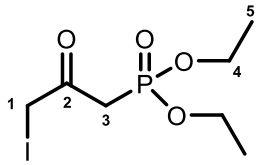
MS (FTMS +p APCI corona Full lock ms) m/z (%): 556.250 (0.2), 555.246 (1.7), 554.243 (8.1), 553.240 $[M+H]^+$ (20.0), 424.181 (17.5), 319.124 (10.0), 279.092 (90.2), 263.097 (71.0), 162.091 (20.9), 130.064 (100.0).

HRMS m/z calculated for $C_{37}H_{34}O_1N_2P_1$ $[M+H]^+$: 553.24033. Found: 553.23937.

diethyl (3-iodo-2-oxopropyl)phosphonate



To as solution of diethyl (3-chloro-2-oxopropyl)phosphonate (1.2 g, 5.3 mmol, 1 eq., 1 ml) in anhydrous acetonitrile (20 ml) was added sodium iodide (2.4 g, 16.0 mmol, 3 eq.) and the mixture was stirred for 6 hours at room temperature. Water was added as quench and the mixture was extracted with dichloromethane. The organic phases were combined and dried over magnesium sulfate, then volatiles were removed *in vacuo* to afford the desired iodo-keto-phosphonate as a slightly yellow oil; 1.7 g (85%).



CAS: /

Formula: $C_7H_{14}IO_4P$

Molecular weight: 320.06 g/mol

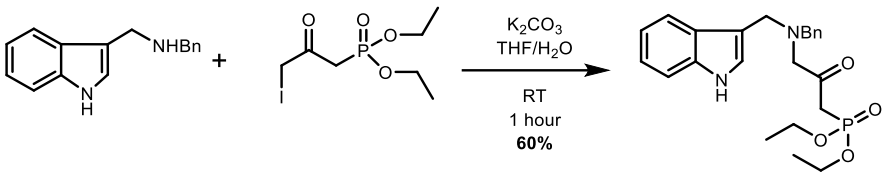
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.26 – 4.07 (m, 4H, **H4**), 4.03 (s, *J* = 3.9 Hz, 2H, **H1**), 3.34 (d, *J* = 22.5 Hz, 2H, **H3**), 1.32 (t, *J* = 7.1 Hz, 6H, **H5**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 194.73 (d, *J* = 5.6 Hz, **C2**), 63.06 (d, *J* = 6.5 Hz, **C4**), 38.95 (d, *J* = 128.1 Hz, **C3**), 16.42 (d, *J* = 6.2 Hz, **C5**), 7.03 (**C1**).

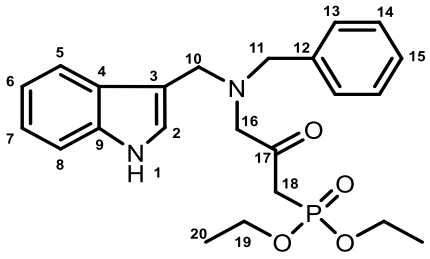
IR (film, cm^{-1}): 2983 (C-H stretching), 2931 (C-H stretching), 2912 (C-H stretching), 1712 (C=O stretching from saturated acyclic ketone), 1477 (CH_2 scissoring), 1444 (CH_3 asymmetric deformation), 1392 (CH_3 symmetric deformation), 1241 (P=O stretching), 1015 (C-O stretching), 965 (P-O stretching).

HRMS m/z calculated for $C_7H_{15}{}^{127}I_1O_4P_1$ $[M+H]^+$: 320.9752. Found: 320.9747.
HRMS m/z calculated for $C_7H_{14}{}^{127}I_1O_4P_1{}^{23}Na_1$ $[M+Na]^+$: 342.9572. Found: 342.9567.

diethyl-(3-(((1H-indol-3-yl)methyl)(benzyl)amino)-2-oxopropyl)phosphonate



To as solution of N-((1H-indol-3-yl)methyl)-1-phenylmethanamine (0.94 g, 4 mmol, 1eq.) and potassium carbonate (0.66 g, 4.8 mmol, 1.2 eq.) in tetrahydrofuran (12 ml) and water (3 ml) was added diethyl (3-iodo-2-oxopropyl)phosphonate (1.28 g, 4 mmol, 1 eq.) at room temperature and the mixture was stirred for 1 hour. Addition of water as quench, the mixture was extracted with dichloromethane and the organic layers were dried over sodium sulfate. All volatiles were removed *in vacuo* and the crude oil was purified by column chromatography using flash silica gel, diethyl ether and ethyl acetate. To afford the desired product as a colourless oil; 1.7 g (60%).



CAS: /

Formula: $C_{23}H_{29}N_2O_4P$

Molecular weight: 428.46 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (bs, 1H, **H1**), 7.71 – 7.66 (m, 1H, **H5**), 7.42 – 7.37 (m, 2H, **H13**), 7.36 – 7.30 (m, 3H, **H8** + **H14**), 7.26 (tt, *J* = 7.1, 1.4 Hz, 1H, **H15**), 7.19 – 7.14 (m, 1H, **H7**), 7.14 – 7.09 (m, 1H, **H6**), 7.07 (d, *J* = 2.4 Hz, 1H, **H2**), 3.99 – 3.88 (m, 4H, **H19**), 3.86 (s, 2H, **H10**), 3.75 (s, 2H, **H11**), 3.36 (s, 2H, **H16**), 2.95 (d, *J* = 22.2 Hz, 2H, **H18**), 1.21 – 1.16 (m, 6H, **H20**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.54 (d, *J* = 6.5 Hz, **C17**), 138.76 (**C12**), 136.60 (**C9**), 129.30 (**C13**), 128.39 (**C14**), 127.65 (**C4**), 127.31 (**C15**), 124.73 (**C2**), 121.95 (**C7**), 119.50 (**C5**), 119.46 (**C6**), 112.02 (**C3**), 111.36 (**C8**), 64.22

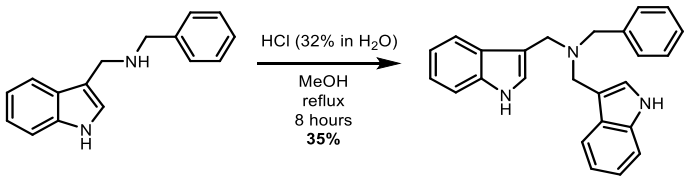
(d, *J* = 1.6 Hz, **C16**), 62.39 (d, *J* = 6.4 Hz, **C19**), 59.59 (**C11**), 50.21 (**C10**), 38.36 (d, *J* = 128.5 Hz, **C18**), 16.23 (d, *J* = 6.1 Hz, **C20**).

IR (film, cm^{-1}): 3405 (O-H stretching of enol form), 3263 (N-H stretching), 3060 (C-H stretching), 3029 (C-H stretching), 2983 (C-H stretching), 2928 (C-H stretching), 2908 (C-H stretching), 2808 (C-H stretching), 1716 (C=O stretching of saturated acyclic ketone), 1619 (C=C aromatic stretching), 1554 (C=C aromatic stretching), 1494 (C=C aromatic stretching), 1454 (CH_2 scissoring), 1237 (P=O stretching + C-N stretching), 1019 (C-O stretching), 967 (P-O stretching), 907, 725 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of mono-substituted aromatic ring), 697 (C-H bending out of plan of mono-substituted aromatic ring).

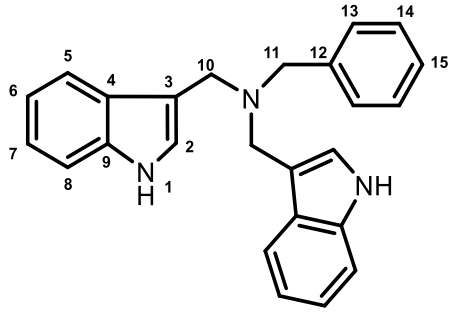
MS (FTMS +p ESI Full ms) m/z (%): 431.199 (0.7), 430.197 (4.6), 429.193 $[M+H]^+$ (18.3), 366.195 (40.0), 300.135 (100.0), 237.138 (12.7), 130.065 (69.8).

HRMS m/z calculated for $C_{23}H_{30}O_4N_2P_1$ $[M+H]^+$: 429.19377. Found: 429.19302.

N,N-bis((1H-indol-3-yl)methyl)-1-phenylmethanamine



To a solution of N-((1H-indol-3-yl)methyl)-1-phenylmethanamine (1.0 g, 4.2 mmol, 1 eq.) in methanol (15 ml) was added aqueous HCl 32% (0.2 ml). The solution was refluxed for 8 hours then the volatiles were removed *in vacuo* to afford a yellow oil. This oil was purified by column chromatography using flash silica gel, methanol and dichloromethane to afford the product as a white solid; 0.54 g (35%).



CAS: /

Formula: $C_{25}H_{23}N_3$

Molecular weight: 365.48 g/mol

MP: 50-52°C **Litt:** /

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (bs, 2H, **H1**), 7.68 (d, *J* = 7.8 Hz, 2H, **H5**), 7.41 (d, *J* = 7.6 Hz, 2H, **H13**), 7.37 – 7.12 (m, 9H, **H2** + **H7** + **H8** + **H14** + **H15**), 7.12 – 7.04 (m, 2H, **H6**), 3.81 (s, 4H, **H10**), 3.64 (s, 2H, **H11**).

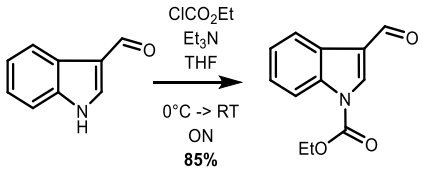
^{13}C NMR (75 MHz, $CDCl_3$) δ 140.56 (**C12**), 136.57 (**C9**), 129.16 (**C13**), 128.21 (**C14**), 128.00 (**C4**), 126.73 (**C15**), 123.49 (**C2**), 122.05 (**C7**), 120.19 (**C5**), 119.40 (**C6**), 114.32 (**C3**), 111.01 (**C8**), 58.26 (**C11**), 49.41 (**C10**).

IR (film, cm^{-1}): 3413 (N-H stretching), 3057 (C-H stretching), 3028 (C-H stretching), 2921 (C-H stretching), 2790 (C-H stretching), 1618 (C=C aromatic stretching), 1556 (C=C aromatic stretching), 1492 (C=C aromatic

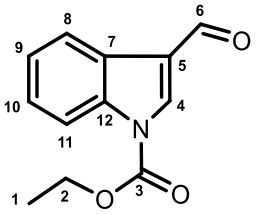
stretching), 1455 (CH_2 scissoring), 1235 (C-N stretching), 739 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of mono-substituted aromatic ring), 699 (C-H bending out of plan of mono-substituted aromatic ring).

HRMS m/z calculated for $C_{25}H_{24}N_3$ $[M+H]^+$: 366.19647. Found: 366.19585.

ethyl 3-formyl-1H-indole-1-carboxylate



Ethyl chloroformate (22.4 g, 0.206 mol, 1.2 eq., 19.7 ml) was added dropwise with stirring to 1H-indole-3-carbaldehyde (25 g, 0.17 mol, 1 eq.) and triethylamine (22.6 g, 0.22 mol, 1.3 eq., 30.2 ml) in tetrahydrofuran (400 ml) at 0°C over 1 hour. The mixture was stirred at this temperature for 2 additional hours then water (10 g, 0.55 mol, 2.7 eq., 10 ml) is added and the stirring continues over night at room temperature. A 1M HCl aqueous solution was added and the resulting solution was vigorously shaken for few seconds then extracted three time with ethyl acetate. The combined organic layers were washed by a saturated solution of sodium bicarbonate in water then dried over sodium sulfate. All volatiles were removed *in vacuo* to afford a yellowish solid; 31.4 g (85%).



CAS: 500995-08-4

Formula: $C_{12}H_{11}NO_3$

Molecular weight: 217.22 g/mol

MP: 69-71°C **Litt**[6]**:** 74°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 1H, **H6**), 8.30 (d, *J* = 7.0 Hz, 1H, **H8**), 8.28 (s, 1H, **H4**), 8.19 (d, *J* = 7.7 Hz, 1H, **H11**), 7.54 – 7.33 (m, 2H, **H9** + **H10**), 4.57 (q, *J* = 7.1 Hz, 2H, **H2**), 1.52 (t, *J* = 7.1 Hz, 3H, **H1**).

[6] Chakrabarty, M.; Basak, R.; Harigaya, Y.; Takayanagi, H. *Tetrahedron* **2005**, *61*, 1793.

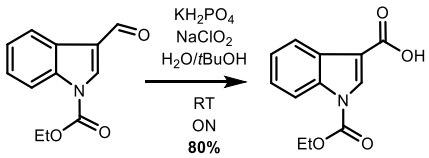
^{13}C NMR (75 MHz, $CDCl_3$) δ 185.85 (**C6**), 150.38 (**C3**), 136.21 (**C4**), 136.09 (**C12**), 126.43 (**C10**), 126.17 (**C7**), 124.97 (**C9**), 122.33 (**C8**), 122.24 (**C5**), 115.27 (**C11**), 64.51 (**C2**), 14.45 (**C1**).

IR (film, cm^{-1}): 2984 (C-H stretching), 2818 (C-H stretching), 1744 (C=O stretching of carbamate), 1671 (C=O stretching), 1549 (C=C stretching), 1479 (C=C stretching), 1449 (CH_2 scissoring), 1222 (C-N stretching), 1088 (C-O stretching), 1000 (C-O stretching), 745 (C-H bending out of plan of para disubstituted aromatic ring).

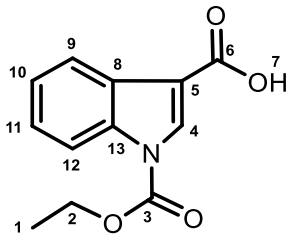
MS (FTMS +p ESI Full ms2) m/z (%): 218.080 $[M+H]^+$ (80.0), 190.049 (33.0), 174.090 (4.0), 146.059 (52.0), 118.065 (100.0), 91.054 (2.0).

HRMS m/z calculated for $C_{12}H_{12}O_3N_1$ $[M+H]^+$: 218.08117. Found: 218.08128.

1-(ethoxycarbonyl)-1H-indole-3-carboxylic acid



To a solution of Ethyl 3-formyl-1H-indole-1-carboxylate (20 g, 92 mmol, 1 eq.) in *tert*-butyl alcohol (200 ml) was added 2-methyl-2-butene (12.9 g, 184 mmol, 2 eq., 19.5 ml) at room temperature. Potassium dihydrogenphosphate (28.2 g, 207 mmol, 2.25 eq.) and sodium chlorite (25 g, 276 mmol, 3 eq.) were dissolved in water (200 ml). When the aqueous solution is free of solid salt, it's added on the organic phase and stirred over night at room temperature. A 1M HCl solution is added to quench the reaction, the resulting mixture was extracted four time with ethyl acetate. The organic phases were combined and dried over sodium sulfate. All the volatiles were removed *in vacuo* to afford a yellow solid. Dry diethyl ether (50 ml) was added to this yellow solid and the mixture was stirred at room temperature. After at least 8 hours, the suspension was filtered and rinsed with diethyl ether, then dried *in vacuo* to afford the off-white product; 17.2 g (80%).



CAS: /

Formula: $C_{12}H_{11}NO_4$

Molecular weight: 233.22 g/mol

MP: 209-211°C **Litt:** /

^{1}H NMR (300 MHz, DMSO) δ 12.82 (s, 1H, **H7**), 8.21 (s, 1H, **H4**), 8.14 (dd, *J* = 7.4, 0.9 Hz, 1H, **H12**), 8.10 (dd, *J* = 7.5, 1.0 Hz, 1H, **H9**), 7.46 – 7.39 (m, 1H, **H11**), 7.40 – 7.33 (m, 1H, **H10**), 4.48 (q, *J* = 7.1 Hz, 2H, **H2**), 1.41 (t, *J* = 7.1 Hz, 3H, **H1**).

^{13}C NMR (75 MHz, DMSO) δ 164.68 (**C6**), 149.86 (**C3**), 135.03 (**C13**), 131.44 (**C4**), 127.31 (**C8**), 125.22 (**C11**), 123.98 (**C10**), 121.33 (**C9**), 114.85 (**C12**), 112.85 (**C5**), 64.07 (**C2**), 13.98 (**C1**).

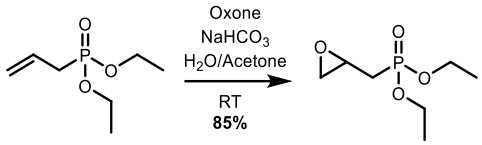
IR (film, cm^{-1}): 2986 (C-H stretching), 2545 (O-H stretching), 1757 (C=O stretching of carbamate), 1670 (C=O stretching), 1555 (C=C stretching), 1487 (C=C stretching), 1284 (C-O acid stretching), 1210 (C-N stretching), 1075 (C-O stretching), 761 (C-H bending out of plan of para disubstituted aromatic ring), 749 (C-H bending out of plan of para disubstituted aromatic ring).

MS (FTMS +p ESI Full ms2) m/z (%): 234.075 $[M+H]^+$ (20.0), 216.065 (2.0), 206.044 (14.0), 190.085 (16.0), 172.075 (2.0), 162.054 (35.0), 146.096 (25.0), 126.58 (5.0), 118.065 (100.0), 91.054 (2.0).

HRMS m/z calculated for $C_{12}H_{12}O_4N_1$ $[M+H]^+$: 234.07608. Found: 234.07613.

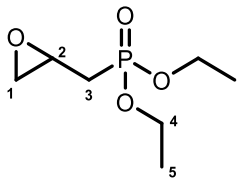
The compound was already described in the literature:
Tsai, A-I.; Lin, C-H.; Chuang, C-P., *Heterocycles*, **2005**, *65*, 2381.

diethyl (oxiran-2-ylmethyl)phosphonate



To a solution of diethyl allylphosphonate (21.1 g, 118 mmol, 1 eq., 20.0 ml) in acetone (200 ml) and water (200 ml) was added first sodium bicarbonate (16.9 g, 200 mmol, 1.7 eq.) and then Oxone (36.4 g, 118 mmol, 1 eq.). The addition of sodium bicarbonate then Oxone were repeated until completion of the reaction (4 additions were need here). Then the mixture was extracted four time with ethyl acetate, the organic phases were combined and dried over magnesium sulfate. The volatiles were removed under low vacuum to afford a colourless oil; 22.9 g (85%).

This product was used without any further purification.



CAS: 7316-37-2

Formula: $C_7H_{15}O_4P$

Molecular weight: 194.16 g/mol

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 – 4.06 (m, 4H, **H4**), 3.25 – 3.14 (m, 1H, **H2**), 2.89 – 2.80 (m, 1H, **H1**), 2.60 (dd, *J* = 4.8, 2.5 Hz, 1H, **H1'**), 2.22 (ddd, *J* = 18.3, 15.2, 5.7 Hz, 1H, **H3**), 1.87 (ddd, *J* = 19.9, 15.2, 6.5 Hz, 1H, **H3'**), 1.35 (t, *J* = 7.0 Hz, 6H, **H5**).

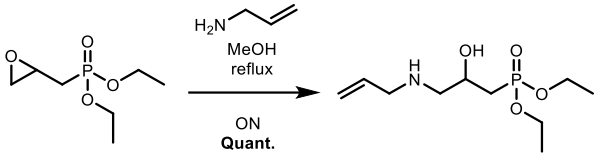
^{13}C NMR (75 MHz, $CDCl_3$) δ 62.07 (d, *J* = 6.4 Hz, **C4**), 47.41 (d, *J* = 7.2 Hz, **C1**), 46.94 (d, *J* = 1.9 Hz, **C2**), 30.30 (d, *J* = 139.0 Hz, **C3**), 16.55 (d, *J* = 6.0 Hz, **C5**).

IR (film, cm^{-1}): 2958 (C-H stretching), 2931 (C-H stretching), 2913 (C-H stretching), 1481 (CH_2 scissoring), 1445 (CH_3 asymmetric deformation), 1395 (CH_3 symmetric deformation), 1273 (C-O stretching), 1220 (P=O

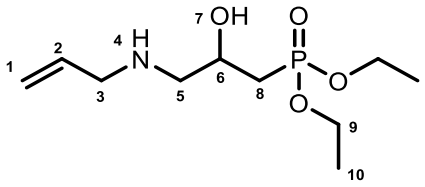
stretching of phosphonate), 1015 (C-O stretching), 959 (P-O stretching), 840.

The compound was already described in the literature:
Arbusow; Lugowkin, *Zhurnal Obshchei Khimii*, **1952**, *22*, 1193.

diethyl (3-(allylamino)-2-hydroxypropyl)phosphonate



To a solution of diethyl (oxiran-2-ylmethyl)phosphonate (20.0 g, 0.10 mol, 1 eq.) in methanol (400 ml) was added allylamine (30.9 g, 0.54 mol, 5.25 eq., 40.5 ml) and the mixture was refluxed overnight. All volatiles were removed under vacuum to afford the desired product as a colourless oil; 25.9 g (quantitative).



CAS: /

Formula: $C_{10}H_{22}NO_4P$

Molecular weight: 251.26 g/mol

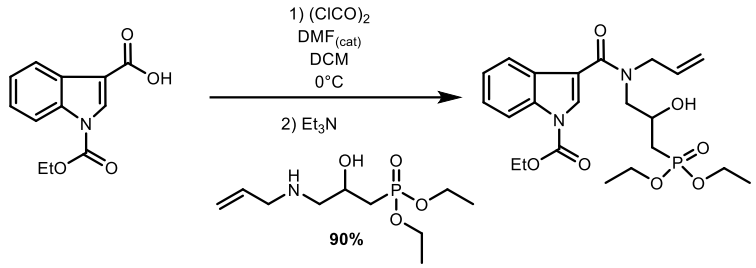
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (ddt, *J* = 16.3, 10.2, 6.0 Hz, 1H, **H2**), 5.19 (ddd, *J* = 17.2, 3.2, 1.6 Hz, 1H, **H1**), 5.11 (ddd, *J* = 10.2, 1.5 Hz, 1H, **H1'**), 4.21 – 4.03 (m, 5H, **H6** + **H9**), 3.36 – 3.21 (m, 2H, **H3**), 3.21 – 2.92 (bs, 2H, **H4** + **H7**), 2.78 (dd, *J* = 12.1, 3.6 Hz, 1H, **H5**), 2.64 (dd, *J* = 12.1, 8.0 Hz, 1H, **H5'**), 1.98 (dqd, *J* = 19.6, 15.3, 6.3 Hz, 2H, **H8**), 1.34 (t, *J* = 7.1 Hz, 6H, **H10**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 136.42 (**C2**), 116.44 (**C1**), 65.22 (d, *J* = 4.0 Hz, **C6**), 61.97 (t, *J* = 6.3 Hz, **C9**), 55.14 (d, *J* = 16.2 Hz, **C5**), 52.13 (s, *J* = 9.5 Hz, **C3**), 31.65 (d, *J* = 139.5 Hz, **C8**), 16.53 (d, *J* = 6.0 Hz, **C10**).

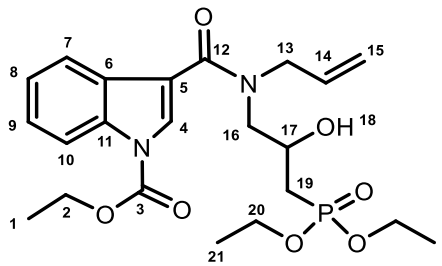
IR (film, cm^{-1}): 3356 (O-H stretching + N-H stretching), 2982 (C-H stretching), 2909 (C-H stretching), 2834 (C-H stretching), 1644 (C=C stretching of mono-substituted alkene), 1444 (CH_3 asymmetric deformation), 1392 (CH_3 symmetric deformation), 1217 (P=O stretching of phosphonate), 1018 (C-O stretching), 958 (P-O stretching)

HRMS m/z calculated for $C_{10}H_{23}O_4N_1P_1$ $[M+H]^+$: 252.13592. Found: 252.13601

ethyl 3-(allyl(3-(diethoxyphosphoryl)-2-hydroxypropyl)carbamoyl)-1H-indole-1-carboxylate



Oxalyl chloride (11.2 g, 88 mmol, 1.25 eq., 7.6 ml) was added dropwise on one hour to a solution of 1-(ethoxycarbonyl)-1H-indole-3-carboxylic acid (16.5 g, 70 mmol, 1 eq.) in dichloromethane (400 ml) at 0°C, followed by addition of dimethylformamide (0.5 ml). The mixture was stirred for two additional hours at room temperature. The solution was cooled to 0°C and triethylamine (21.5 g, 212 mmol, 3 eq., 28.6 ml) was added on half an hour, followed by addition of diethyl (3-(allylamino)-2-hydroxypropyl)phosphonate (26.2 g, 104 mmol, 1.47 eq.) in dichloromethane (10 ml) on less than one minute. The resulting mixture was stirred for four additional hours at room temperature. The solvents were removed under vacuum and the oil was dissolved in ethyl acetate and 1M HCl aqueous solution. The biphasic system was vigorously shaken, then separated. The aqueous phase was extracted three more time with ethyl acetate, all four organic phases were combined and dried over sodium sulfate. All volatiles were removed *in vacuo* to afford the desired product as a brown solid; 29.7 g (90%).



CAS: /

Formula: $C_{22}H_{31}N_2O_7P$

Molecular weight: 466.47 g/mol

MP: 53-56°C **Litt:** /

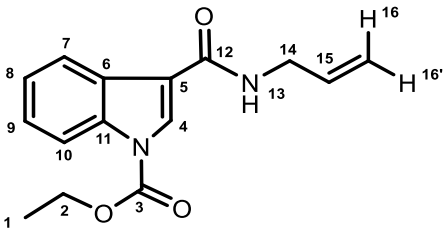
^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.1 Hz, 1H, **H10**), 7.91 (s, 1H, **H4**), 7.77 (d, *J* = 7.4 Hz, 1H, **H7**), 7.43 – 7.35 (m, 1H, **H9**), 7.35 – 7.28 (m, 1H, **H8**), 5.91 – 5.75 (m, 1H, **H14**), 5.35 – 5.17 (m, 2H, **H15**), 4.51 (q, *J* = 7.1 Hz, 2H, **H2**), 4.45 – 4.20 (m, 3H, **H13** + **H17**), 4.21 – 4.04 (m, 4H, **H20**), 3.70 (s, 2H, **H16**), 2.04 (bs, 2H, **H19**), 1.47 (t, *J* = 7.1 Hz, 3H, **H1**), 1.33 (tt, *J* = 9.0, 4.5 Hz, 6H, **H21**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.68 (**C12**), 150.75 (**C3**), 134.96 (**C11**), 133.58 (**C14**), 128.62 (**C6**), 125.48 (**C4**+**C9**), 123.89 (**C8**), 121.08 (**C7**), 117.67 (**C15**), 115.93 (**C5**), 115.24 (**C10**), 66.60 (**C17**), 63.85 (**C2**), 62.10 (t, *J* = 6.6 Hz, **C20**), 53.24 (**C13**), 52.46 (**C16**), 31.90 (d, *J* = 138.4 Hz, **C19**), 16.49 (d, *J* = 5.6 Hz, **C21**), 14.40 (**C1**).

IR (cm^{-1}): 3366 (O-H stretching), 2983 (C-H stretching), 2933 (C-H stretching), 1743 (C=O stretching of carbamate), 1622 (C=O stretching), 1559 (C=C aromatic stretching), 1453 (CH_2 scissoring), 1239 (P=O stretching), 1211 (O-CH_2 stretching), 1024 (P-O stretching), 765 (C-H bending out of plan of para disubstituted aromatic ring), 750 (C-H bending out of plan of para disubstituted aromatic ring).

HRMS m/z calculated for $C_{22}H_{32}O_7N_2P_1$ $[M+H]^+$: 467.19416. Found: 467.19409

ethyl 3-(allylcarbamoyl)-1H-indole-1-carboxylate



CAS: /

Formula: $C_{15}H_{16}N_2O_3$

Molecular weight: 272.30 g/mol

Off-white solid

MP: 114-116°C **Litt:** /

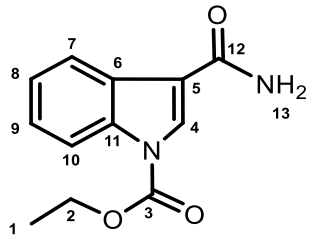
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.1 Hz, 1H, **H10**), 8.11 (s, 1H, **H4**), 8.04 (dd, *J* = 7.1, 1.2 Hz, 1H, **H7**), 7.43 – 7.38 (m, 1H, **H9**), 7.38 – 7.33 (m, 1H, **H8**), 6.04 (s, 1H, **H13**), 5.98 (ddt, *J* = 17.1, 10.2, 5.7 Hz, 1H, **H15**), 5.30 (ddd, *J* = 17.2, 3.0, 1.6 Hz, 1H, **H16**), 5.22 (dq, *J* = 10.2, 1.4 Hz, 1H, **H16'**), 4.53 (q, *J* = 7.1 Hz, 2H, **H2**), 4.13 (tt, *J* = 5.8, 1.5 Hz, 2H, **H14**), 1.49 (t, *J* = 7.1 Hz, 3H, **H1**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.03 (**C12**), 150.45 (**C3**), 135.32 (**C11**), 134.26 (**C15**), 127.48 (**C6**), 127.25 (**C4**), 125.16 (**C9**), 123.80 (**C8**), 121.13 (**C7**), 116.49 (**C5**), 116.34 (**C16**), 115.07 (**C10**), 63.79 (**C2**), 41.95 (**C14**), 14.21 (**C1**).

IR (cm^{-1}): 3274 (N-H stretching), 3080 (C-H stretching), 3056 (C-H stretching), 2988 (C-H stretching), 2922 (C-H stretching), 1741 (C=O stretching of carbamate), 1632 (C=C stretching of mono-substituted alkene), 1560 (C=C aromatic stretching), 1530 (C=C aromatic stretching), 1487 (CH_2 scissoring), 1451 (CH_2 scissoring), 1430 (CH_3 asymmetric deformation), 1385 (CH_3 symmetric deformation), 1276 (C-H bending of mono-substituted alkene), 1242 (C-N stretching), 763 (C-H bending out of plan), 749 (C-H bending out of plan of ortho di-substituted aromatic ring).

HRMS m/z calculated for $C_{15}H_{17}O_3N_2$ $[M+H]^+$: 273.123369. Found: 273.123284.

ethyl 3-carbamoyl-1H-indole-1-carboxylate



CAS: /

Formula: $C_{12}H_{12}N_2O_3$

Molecular weight: 232.24 g/mol

Off-white solid

MP: 222-224°C **Litt:** /

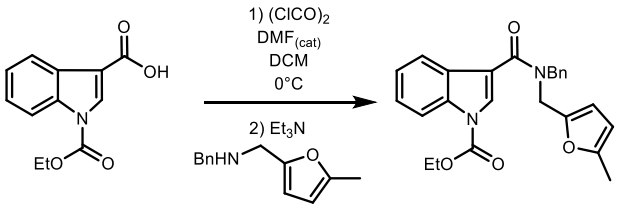
^{1}H NMR (400 MHz, DMSO) δ 8.50 (s, 1H, **H4)**, 8.25 (d, *J* = 7.7 Hz, 1H, **H7**), 8.11 (d, *J* = 8.2 Hz, 1H, **H10**), 7.87 (bs, 1H, **H13**), 7.41 – 7.35 (m, 1H, **H9**), 7.31 (t, *J* = 7.1 Hz, 1H, **H8**), 7.17 (bs, 1H, **H13'**), 4.49 (q, *J* = 7.1 Hz, 2H, **H2**), 1.42 (t, *J* = 7.1 Hz, 3H, **H1**).

^{13}C NMR (100 MHz, DMSO) δ 164.97 (**C12**), 150.22 (**C3**), 134.82 (**C11**), 128.29 (**C6**), 128.07 (**C4**), 124.87 (**C9**), 123.53 (**C8**), 122.02 (**C7**), 115.42 (**C5**), 114.60 (**C10**), 63.82 (**C2**), 14.11 (**C1**).

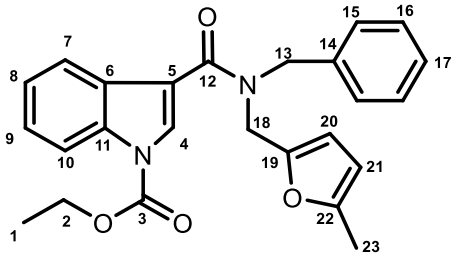
IR (cm^{-1}): 3422 (N-H stretching), 3158 (C-H stretching), 3089 (C-H stretching), 3053 (C-H stretching), 2982 (C-H stretching), 1733 (C=O stretching of carbamate), 1660 (C=O stretching of primary amide), 1624 (NH_2 scissoring), 1451 (CH_2 scissoring), 1402, 1382 (CH_3 symmetric deformation), 1309 (C-C stretching), 1250 (C-N stretching), 760 (C-H bending out of plan), 743 (C-H bending out of plan of ortho di-substituted aromatic ring).

HRMS m/z calculated for $C_{12}H_{13}O_3N_2$ $[M+H]^+$: 233.092069. Found: 233.091923.

ethyl 3-(benzyl ((5-methylfuran-2-yl)methyl)carbamoyl) -1H-indole -1-carboxylate



To a solution of 1-(ethoxycarbonyl)-1H-indole-3-carboxylic acid (10 g, 43 mmol, 1 eq.) in dichloromethane (200 ml) and dimethylformamide (0.5 ml) at room temperature was added oxalyl chloride (6 g, 47.3 mmol, 1.1 eq, 4.05 ml). The mixture was stirred for 1 hour then cool to 0°C. A dropwise addition of triethylamine (10.8 g, 107 mmol, 2.5 eq., 14.5 ml) on 10 minutes followed by stirring for additional 10 minutes at 0°C. A dropwise addition of N-benzyl-1-(5-methylfuran-2-yl)methanamine (9.9 g, 49 mmol, 1.15 eq., 9.4 ml) at 0°C then the mixture was allowed to evolve towards room temperature for 5 hours. The solvent was removed under vacuum then the viscous oil was dissolved in ethyl acetate and 1M aqueous HCl and extracted with ethyl acetate. The organics phases were combined and dried over sodium sulfate. The volatiles were removed *in vacuo* to afford the desired product as a sticky yellow oil; 16.1 g (90%).



CAS: /

Formula: $C_{25}H_{24}N_2O_4$

Molecular weight: 416.47 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 7.9 Hz, 1H, **H10**), 7.82 (d, *J* = 7.2 Hz, 1H, **H7**), 7.44 – 7.27 (m, 8H, **H4** + **H8** + **H9** + **H15** + **H16** + **H17**), 6.11 (s, 1H, **H20**), 5.92 (dd, *J* = 3.0, 0.9 Hz, 1H, **H21**), 4.73 (s, 2H, **H13**), 4.65 – 4.31 (m, 4H, **H2** + **H18**), 2.30 (d, *J* = 0.6 Hz, 3H, **H23**), 1.45 (t, *J* = 6.3 Hz, 3H, **H1**).

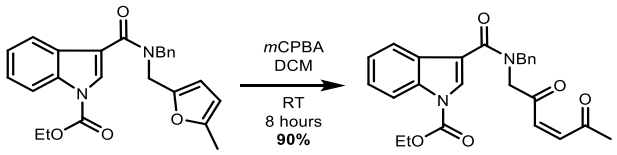
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.06 (**C12**), 152.34 (bs, **C22**), 150.59 (**C3**), 147.97 (bs, **C19**), 136.93 (**C14**), 134.96 (**C11**), 128.69 (**C6** + **C15** + **C16**), 127.48 (**C17**), 125.67 (bs, **C4**), 125.30 (**C9**), 123.70 (**C8**), 120.98 (**C7**), 116.07 (**C5**), 115.13 (**C10**), 109.97 (**C20**), 106.21 (**C21**), 63.62 (**C2**), 47.35 (bs, **C13**), 44.81 (bs, **C18**), 14.25 (**C1**), 13.55 (**C23**).

IR (film, cm^{-1}): 3031 (C-H stretching), 2984 (C-H stretching), 2922(C-H stretching), 1742 (C=O stretching of carbamate), 1627 (C=O stretching of tertiary amide), 1560 (C=C aromatic stretching), 1451 (CH_2 scissoring), 1423 (CH_3 asymmetric deformation), 1398 (CH_3 symmetric deformation), 1238 (C-N stretching), 1210 (C-N stretching), 907, 764 (C-H bending out of plan of mono-substituted aromatic ring), 723 (C-H bending out of plan of ortho di-substituted aromatic ring), 696 (C-H bending out of plan of mono-substituted aromatic ring), 645 (C-H bending).

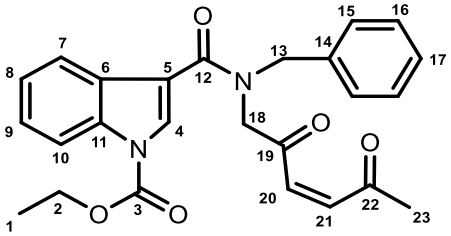
MS (FTMS +p ESI Full ms) m/z (%): 833.353 $[2M+H]^+$ (100.0), 439.162 $[M+Na]^+$ (15.0), 417.180 $[M+H]^+$ (50.2), 323.139 (10.9), 296.164 (71.2), 95.049 (17.3).

HRMS m/z calculated for $C_{25}H_{25}O_4N_2$ $[M+H]^+$: 417.180884. Found: 417.180773.

ethyl (*Z*)-3-(benzyl(2,5-dioxohex-3-en-1-yl)carbamoyl)-1H-indole-1-carboxylate



To a solution of ethyl 3-(benzyl((5-methylfuran-2-yl)methyl)carbamoyl)-1H-indole-1-carboxylate (4.6 g, 11 mmol, 1 eq.) in dichloromethane (60 ml) at 0°C was added solid *meta*-chloroperoxybenzoic acid (2.72 g, 12.1 mmol, 1.1 eq.). The reaction was allowed to warm at room temperature and stirred for 8 hours. Quench was made by addition of a saturated solution of sodium hydrogencarbonate in water, then extracted by dichloromethane. The organic phases were combined and dried over sodium sulfate and the volatiles were removed *in vacuo* to afford the desired product as a sticky yellow oil; 4.3 g (90%).



CAS: /

Formula: $C_{25}H_{24}N_2O_5$

Molecular weight: 432.47 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 1H, **H10**), 7.94 (d, *J* = 4.8 Hz, 1H, H, **H7**), 7.81 (s, 1H, **H4**), 7.49 – 7.18 (m, 7H, **H8** + **H9** + **H15** + **H16** + **H17**), 6.53 – 6.33 (m, 2H, **H20** + **H21**), 4.83 (s, 2H, **H13**), 4.57 – 4.36 (m, 4H, **H2** + **H18**), 2.30 (s, 3H, **H23**), 1.42 (t, *J* = 7.0 Hz, 3H, **H1**).

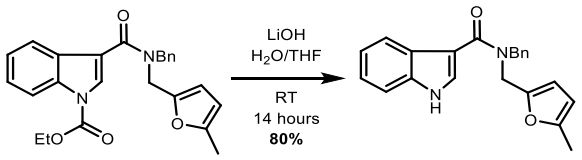
^{13}C NMR (100 MHz, $CDCl_3$) δ 199.74 (**C22**), 198.06 (**C19**), 166.85 (**C12**), 150.56 (**C3**), 136.70 (**C11**), 135.88 (**C20/C21**), 135.49 (**C20/21**), 134.94 (**C11**), 128.95 (**C16**), 128.47 (**C15**), 127.82 (**C17**), 127.07 (**C4**), 125.52 (**C9**), 123.97 (**C8**), 121.29 (**C7**), 115.72 (**C5**), 115.22 (**C10**), 63.76 (**C2**), 53.89 (**C18**), 53.66 (**C13**), 29.96 (**C23**), 14.30 (**C1**).

IR (film, cm^{-1}): 3057 (C-H stretching), 3030 (C-H stretching), 2983 (C-H stretching), 2932 (C-H stretching), 1742 (C=O stretching of carbamate), 1712 (C=O stretching), 1697 (C=O stretching), 1632 (C=O stretching of tertiary amide + C=C stretching of *cis* di-substituted alkene), 1557 (C=C aromatic stretching), 1452 (CH_2 scissoring), 1429 (CH_3 asymmetric deformation), 1397 (CH_3 symmetric deformation), 1238 (C-N stretching), 1208 (C-N stretching), 1090 (C-O stretching), 764 (C-H bending out of plan of mono-substituted aromatic ring), 749 (C-H bending out of plan of ortho di-substituted aromatic ring), 732 (C-H bending out of plan of *cis* di-substituted alkene), 697 (C-H bending out of plan of mono-substituted aromatic ring).

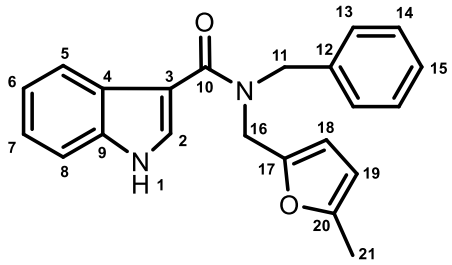
MS (FTMS +p ESI Full ms) m/z (%): 455.157 $[M+Na]^+$ (12.8), 436.184 (0.6), 435.181 (4.5), 434.179 (27.6), 433.175 $[M+H]^+$ (100.0), 415.165 (5.0), 312.159 (7.5), 216.065 (5.0), 144.044 (5.2).

HRMS m/z calculated for $C_{25}H_{25}O_5N_2$ $[M+H]^+$: 433.175798. Found: 433.175784.

N-benzyl-N-((5-methylfuran-2-yl)methyl)-1H-indole-3-carboxamide



To a solution of (7.1 g, 17 mmol, 1 eq.) in tetrahydrofuran (100 ml) at room temperature was added a solution of lithium hydroxide (0.81 g, 34mmol, 2 eq.) in water (100 ml). The mixture was stirred for 14 hours at room temperature then quenched by addition of a saturated solution of ammonium chloride in water. After extraction with ethyl acetate, the organic phases were combined and dried over sodium sulfate. All volatiles were removed *in vacuo* and the product was purified by precipitation in acetone and water to afford the desired compound as an off-white solid; 4.68 g (80%).



CAS: /

Formula: $C_{22}H_{20}N_2O_2$

Molecular weight: 344.41 g/mol

MP: 121-124°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.39 (s, 1H, **H1**), 7.89 (d, *J* = 7.9 Hz, 1H, **H5**), 7.37 – 7.16 (m, 5H, **H13** + **H14** + **H15**), 7.16 – 6.98 (m, 4H, **H2** + **H6** + **H7** + **H8**), 6.03 (s, 1H, **H18**), 5.96 – 5.76 (m, 1H, **H19**), 4.74 (s, 2H, **H11**), 4.56 (s, 2H, **H16**), 2.21 (s, 3H, **H21**).

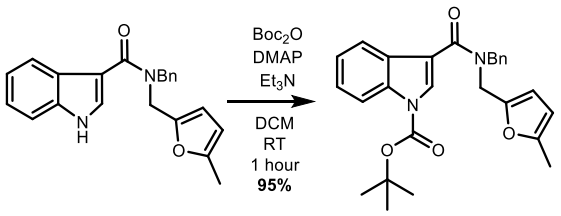
^{13}C NMR (75 MHz, $CDCl_3$) δ 168.74 (**C10**), 152.19 (**C20**), 148.55 (**C17**), 137.23 (**C12**), 136.06 (**C9**), 128.71 (**C14**), 127.70 (bs, **C13**), 127.40 (**C15**), 126.85 (**C2**), 126.44 (**C4**), 122.45 (**C7**), 120.80 (**C6**), 120.28 (**C5**), 112.10 (**C8**), 109.74 (**C18**), 109.62 (**C3**), 106.26 (**C19**), 48.89 (bs, **C11**), 44.15 (bs, **C16**), 13.62 (**C21**).

IR (film, cm^{-1}): 3213 (N-H stretching), 3061 (C-H stretching), 2921 (C-H stretching), 1594 (C=C aromatic stretching), 1573 (C=C aromatic stretching), 1525 (C=C aromatic stretching), 1494 (C=C aromatic stretching), 1450 (CH_2 scissoring), 1183 (C-N stretching), 1020 (C-O stretching), 976, 780 (C-H bending out of plan), 733 (C-H bending out of plan of ortho di-substituted aromatic ring+ C-H bending out of plan of mono-substituted aromatic ring), 696 (C-H bending out of plan of mono-substituted aromatic ring).

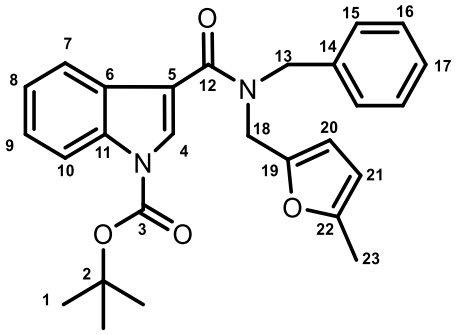
MS (FTMS +p ESI Full ms2) m/z (%): 367.141 $[M+Na]^+$ (20.0), 345.159 $[M+H]^+$ (2.0), 263.011 (5.0), 251.117 (45.0), 144.044 (100.0), 95.049 (46.0).

HRMS m/z calculated for $C_{22}H_{21}O_2N_2$ $[M+H]^+$: 345.15975**.** Found: 345.15975.

tert-butyl 3-(benzyl((5-methylfuran-2-yl)methyl)carbamoyl)-1H-indole-1-carboxylate



To a solution of N-benzyl-N-((5-methylfuran-2-yl)methyl)-1H-indole-3-carboxamide (2 g, 5.8 mmol, 1 eq.) in dichloromethane (40 ml) and triethylamine (0.75 g, 7.4 mmol, 1.25 eq., 1 ml) at room temperature was added 4-dimethylaminopyridine (0.14 g, 0.6 mmol, 0.2 eq.) followed by di-*tert*-butyl dicarbonate (1.4 g, 6.4 mmol, 1.1 eq.). The mixture was stirred for 1 hour at room temperature then water (5 ml) was added as quench. After stirring for 2 additional hours the mixture was decanted and extracted with dichloromethane. The organic phases were combined and dried over sodium sulfate and the volatiles were removed *in vacuo* to afford the desired product as a sticky slightly yellow oil; 2.45 g (95%).



CAS: /

Formula: $C_{27}H_{28}N_2O_4$

Molecular weight: 444.53 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.9 Hz, 1H, **H10**), 7.85 – 7.77 (m, 1H, **H7**), 7.48 – 7.27 (m, 8H, **H4** + **H8** + **H9** + **H15** + **H16** + **H17**), 6.12 (s, 1H, **H20**), 5.92 (dd, *J* = 3.0, 0.9 Hz, 1H, **H21**), 4.74 (s, 2H, **H13**), 4.50 (s, 2H, **18**), 2.29 (d, *J* = 0.6 Hz, 3H, **H23**), 1.63 (s, 9H, **H1**).

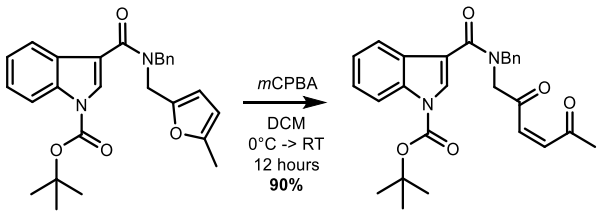
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.33 (**C12**), 152.39 (**C22**), 149.29 (**C3**), 148.22 (**C19**), 137.07 (**C14**), 135.04 (**C11**), 128.77 (**C6** + **C16** + **C17**), 127.53 (**C15**), 126.06 (bs, **C4**), 125.15 (**C9**), 123.52 (**C8**), 121.00 (**C7**), 115.53 (**C5**), 115.23 (**C10**), 109.91 (**C20**), 106.26 (**C21**), 84.45 (**C2**), 47.41 (bs, **C13**), 45.01 (bs, **C18**), 28.12 (**C1**), 13.67 (**C23**).

IR (film, cm^{-1}): 3030 (C-H stretching), 2980 (C-H stretching), 2924 (C-H stretching), 1738 (C=O stretching of carbamate), 1627 (C=O stretching of tertiary amide), 1558 (C=C aromatic stretching), 1450 (CH_2 scissoring), 1422 (CH_3 asymmetric deformation), 1368 (CH_3 symmetric deformation of *tert*-butyl), 1246 (C-N stretching), 1148, 907, 767 (C-H bending out of plan of mono-substituted aromatic ring), 724 (C-H bending out of plan of ortho di-substituted aromatic ring), 696 (C-H bending out of plan of mono-substituted aromatic ring).

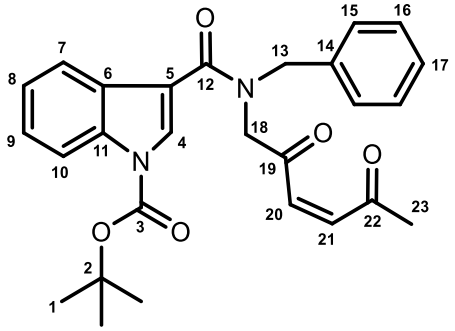
MS (FTMS +p ESI Full ms) m/z (%): 467.194 $[M+Na]^+$ (12.1), 448.221 (0.6), 447.218 (5.0), 446.215 (29.8), 445.212 $[M+H]^+$ (100.0), 355.201 (2.0), 295.107 (7.1), 144.044 (10.2), 95.049 (4.1).

HRMS m/z calculated for $C_{27}H_{29}O_4N_2$ $[M+H]^+$: 445.212184. Found: 445.212134.

tert-butyl (*Z*)-3-(benzyl(2,5-dioxohex-3-en-1-yl)carbamoyl)-1H-indole-1-carboxylate



To a solution of *tert*-butyl 3-(benzyl((5-methylfuran-2-yl)methyl)carbamoyl)-1H-indole-1-carboxylate (2.58 g , 5.8 mmol, 1 eq.) in dichloromethane (20 ml) at 0°C was added solid *meta*-chloroperoxybenzoic acid (1.49 g, 6.6 mmol, 1.15 eq.). The reaction was allowed to warm at room temperature and stirred for 12 hours. Quench was made by addition of a saturated solution of sodium hydrogencarbonate in water, then extracted by dichloromethane. The organic phases were combined and dried over sodium sulfate and the volatiles were removed *in vacuo* to afford the desired product as a slightly yellow sticky solid; 2.4 g (90%).



CAS: /

Formula: $C_{27}H_{28}N_2O_5$

Molecular weight: 460.53 g/mol

MP: 33-34°C **Litt:** /

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.3 Hz, 1H, **H10**), 7.94 (s, 1H, **H7**), 7.77 (s, 1H, **H4**), 7.53 – 7.19 (m, 7H, **H8** + **H9** + **H15** + **H16** + **H17**), 6.54 – 6.31 (m, 2H, **H20** + **H21**), 4.85 (s, 2H, **H13**), 4.41 (s, 2H, **H18**), 2.30 (s, 3H, **H23**), 1.60 (s, 9H, **H1**).

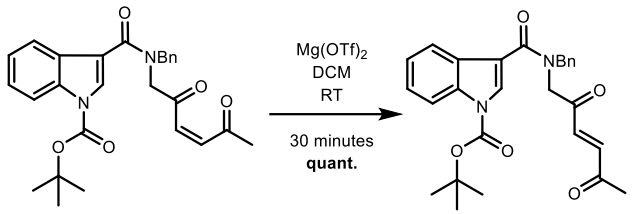
^{13}C NMR (100 MHz, $CDCl_3$) δ 199.77 (**C22**), 198.18 (**C19**), 167.09 (**C12**), 149.17 (**C3**), 136.79 (**C14**), 135.92 (**C20/21**), 135.50 (**C20/21**), 135.00 (**C11**), 128.99 (**C16**), 128.53 (**C6**), 127.83 (**C15**), 127.01 (**C4**), 126.11 (**C17**), 125.32 (**C9**), 123.75 (**C8**), 121.29 (**C7**), 115.24 (**C10**), 114.87 (**C5**), 84.63 (**C2**), 53.94 (**C18**), 53.54 (**C13**), 30.00 (**C23**), 28.11 (**C1**).

IR (cm^{-1}): 3030 (C-H stretching), 2980 (C-H stretching), 2932 (C-H stretching), 1737 (C=O stretching), 1715 (C=O stretching), 1698 (C=O stretching), 1629 (C=O stretching of tertiary amide + C=C stretching of *cis* di-substituted alkene), 1584 (C=C aromatic stretching), 1556 (C=C aromatic stretching), 1496 (C=C aromatic stretching), 1451 (CH_2 scissoring), 1429 (CH_3 asymmetric deformation), 1362 (CH_3 deformation of *tert*-butyl), 1244 (C-N stretching), 1208 (C-N stretching), 1149 (C-O stretching), 1088 (C-O stretching), 767 (C-H bending out of plan of mono-substituted aromatic ring), 724 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of *cis* di-substituted alkene), 696 (C-H bending out of plan of mono-substituted aromatic ring).

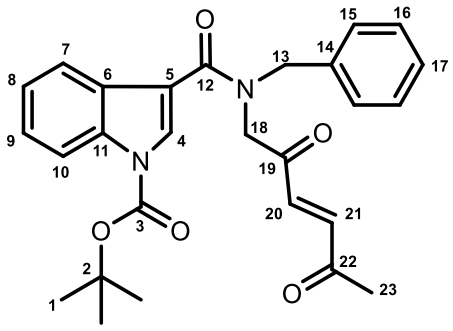
MS (FTMS +p ESI Full ms) m/z (%): 461.207 $[M+H]^+$ (2.5), 405.143 (18.3), 387.132 (14.2), 244.096 (11.7), 218.117 (46.1), 200.106 (63.4), 188.033 (100.0), 154.049 (7.3), 144.044 (39.7), 120.080 (46.2), 91.054 (23.1).

HRMS m/z calculated for $C_{27}H_{29}O_5N_2$ $[M+H]^+$: 461.207098. Found: 461.207081.

tert-butyl (*E*)-3-(benzyl(2,5-dioxohex-3-en-1-yl)carbamoyl)-1H-indole-1-carboxylate



To a solution of *tert*-butyl (*Z*)-3-(benzyl(2,5-dioxohex-3-en-1-yl)carbamoyl)-1H-indole-1-carboxylate (0.46 g, 1 mmol, 1 eq.) in dichloromethane (15 ml) at room temperature was added magnesium triflate (0.39 g, 1.2 mmol, 1.2 eq.) and the solution was stirred for 30 minutes. Addition of a saturated solution of sodium hydrogencarbonate in water as quench followed by extraction with dichloromethane. The organic phases were combined and dried over sodium sulfate, the solvent was removed *in vacuo* to afford the desired product as a sticky yellow solid; 0.46 g (quantitative).



CAS: /

Formula: $C_{27}H_{28}N_2O_5$

Molecular weight: 460.53 g/mol

MP: 33-35°C **Litt:** /

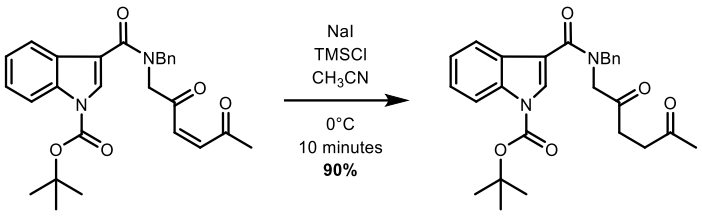
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.9 Hz, 1H, **H10**), 7.93 (s, 1H, **H7**), 7.80 (s, 1H, **H4**), 7.42 – 7.28 (m, 5H, **H8** + **H9** + **H16** + **H17**), 7.23 (s, 2H, **H15**), 6.91 (s, 2H, **H20** + **H21**), 4.80 (s, 2H, **H13**), 4.51 (s, 2H, **H18**), 2.35 (s, 3H, **H23**), 1.60 (s, 9H, **H1**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 197.81 (**C22**), 194.65 (**C19**), 166.91 (**C12**), 149.00 (**C3**), 137.62 (**C20**), 136.20 (**C14**), 134.88 (**C11**), 134.41 (**C21**), 129.02 (**C16**), 128.37 (**C6**), 127.93 (**C17**), 126.86 (**C15**), 126.07 (**C4**), 125.27 (**C9**), 123.68 (**C8**), 121.06 (**C7**), 115.18 (**C10**), 114.59 (**C5**), 84.60 (**C2**), 53.86 (**C13**), 53.48 (**C18**), 27.97 (**C21**).

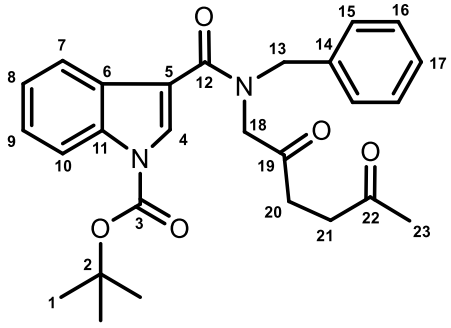
IR (cm^{-1}): 3058 (C-H stretching), 3030 (C-H stretching), 2980 (C-H stretching), 2932 (C-H stretching), 1737 (C=O stretching of carbamate), 1691 (C=O stretching), 1683 (C=O stretching), 1629 (C=O stretching of tertiary amide + C=C stretching of *trans* di-substituted alkene), 1556 (C=C aromatic stretching), 1479 (CH_2 scissoring), 1451 (CH_2 scissoring), 1429 (CH_3 asymmetric deformation), 1360 (CH_3 deformation of *tert*-butyl), 1244 (C-N stretching), 1208 (C-N stretching), 1147 (C-O stretching), 1088 (C-O stretching), 970 (C-H bending out of plan of trans di-substituted alkene), 767 (C-H bending out of plan of mono-substituted aromatic ring), 724 (C-H bending out of plan of ortho di-substituted aromatic ring), 698 (C-H bending out of plan of mono-substituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{29}O_5N_2$ $[M+H]^+$: 461.207098. Found: 461.2070.
HRMS m/z calculated for $C_{27}H_{28}O_5N_2{}^{23}Na_1$ $[M+Na]^+$: 483.1895. Found: 483.1889.

tert-butyl 3-(benzyl(2,5-dioxohexyl)carbamoyl)-1H-indole-1-carboxylate



To a solution of *tert*-butyl (*Z*)-3-(benzyl(2,5-dioxohex-3-en-1-yl)carbamoyl)-1H-indole-1-carboxylate (0.46 g, 1 mmol, 1 eq.) in anhydrous acetonitrile at 0°C was added sodium iodide (0.30 g, 2 mmol, 2 eq.) followed by dropwise addition of trimethylchlorosilane (0.22 g, 2 mmol, 2 eq., 0.25 ml). The mixture was stirred at 0°C for 10 minutes then purred on dichloromethane and a saturated solution of sodium thiosulfate and extracted with dichloromethane. The organic phases were combined, dried over magnesium sulfate and the volatiles were removed *in vacuo* to afford the desired diketone as colourless oil; 0.42 g (90%).



CAS: /

Formula: $C_{27}H_{30}N_2O_5$

Molecular weight: 462.54 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.1 Hz, 1H, **H10**), 7.93 (bs, 1H, **H7**), 7.77 (s, 1H, **H4**), 7.42 – 7.16 (m, 7H, **H8** + **H9** + **H15** + **H16** + **H17**), 4.75 (s, 2H, **H13**), 4.34 (s, 2H, **H18**), 2.83 (bs, 2H, **H21**), 2.71 (bs, 2H, **H20**), 2.20 (s, 3H, **H23**), 1.61 (s, 9H, **H1**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 206.81 (**C22**), 203.89 (**C19**), 166.70 (**C12**), 148.97 (**C3**), 136.49 (**C14**), 134.79 (**C11**), 128.84 (**C16**), 128.39 (**C6**), 127.67 (**C17**), 126.82 (**C15**), 125.76 (**C4**), 125.09 (**C9**), 123.51 (**C8**), 121.08 (**C7**),

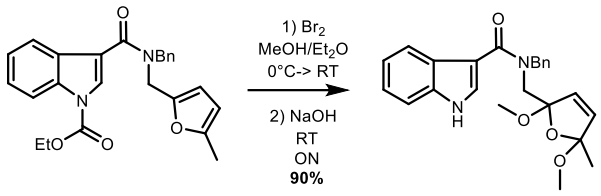
115.04 (**C10**), 114.85 (**C5**), 84.39 (**C2**), 54.11 (**C18**), 53.73 (**C13**), 37.00 (**C21**), 33.44 (**C20**), 29.57 (**C23**), 27.90 (**C1**).

IR (film, cm^{-1}): 3059 (C-H stretching), 3030 (C-H stretching), 2979 (C-H stretching), 2931 (C-H stretching), 1737 (C=O stretching of carbamate), 1715 (C=O stretching), 1633 (C=O stretching of tertiary amide), 1557 (C=C aromatic stretching), 1479 (CH_2 scissoring), 1451 (CH_2 scissoring), 1429 (CH_3 asymmetric deformation), 1363 (CH_3 deformation of *tert*-butyl), 1245 (C-N stretching), 1209 (C-N stretching), 1150 (C-O stretching), 1089 (C-O stretching), 767 (C-H bending out of plan of mono-substituted aromatic ring), 730 (C-H bending out of plan of ortho di-substituted aromatic ring), 698 (C-H bending out of plan of mono-substituted aromatic ring).

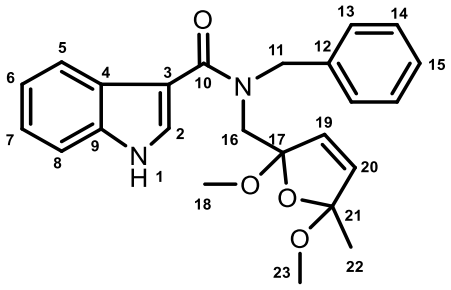
MS (FTMS +p ESI Full ms) m/z (%): 485.205 **$[M+Na]^+$** (55.5), 466.231 (0.7), 465.228 (5.2), 464.226 (29.9), 463.222 **$[M+H]^+$** (100.0), 407.160 (6.0), 234.091 (17.2), 220.133 (95.6), 91.055 (8.5).

HRMS m/z calculated for $C_{27}H_{31}O_5N_2$ $[M+H]^+$: 463.222749. Found: 463.223422.

N-benzyl-N-((2,5-dimethoxy-5-methyl-2,5-dihydrofuran-2-yl)methyl)-1H-indole-3-carboxamide



To a solution of N-benzyl-N-((5-methylfuran-2-yl)methyl)-1H-indole-3-carboxamide (1.78 g, 4.28 mmol, 1 eq.) in methanol (14 ml) and diethyl ether (10 ml) at 0°C was added sodium hydrogencarbonate (1.3 g, 15 mmol, 3.5 eq.) then bromine (0.75 g, 4.7 mmol, 1.1 eq., 0.24 ml) in methanol (1 ml) was added drop wisely. The solution was stirred for 20 minutes at 0°C then was allowed to evolve towards room temperature for 40 minutes. Solid sodium hydroxide (0.68 g, 17 mmol, 4 eq.) was added, and the solution was stirred over night at room temperature. Quench was performed by addition of water and diethyl ether, the resulting biphasic mixture was extracted with another portion of diethyl ether. The organic phases were combined and dried over sodium sulfate. All volatiles were removed *in vacuo* to afford a slightly brown solid; 1.56 g (90%).



CAS: /

Formula: $C_{24}H_{26}N_2O_4$

Molecular weight: 406.48 g/mol

MP: 60-63°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 10.37 (s, 1H, **H1**), 7.83 (s, 1H, **H5**), 7.53 – 6.83 (m, 9H, **H2** + **H6** + **H7** + **H8** + **H13** + **H14** + **H15**), 5.93 (s, 2H, **H19** + **H20**), 4.95 (s, 2H, **H11**), 4.18 – 3.54 (m, 2H, **H16**), 3.49 – 2.95 (m, 6H, **H18** + **H23**), 1.76 – 1.22 (m, 3H, **H22**).

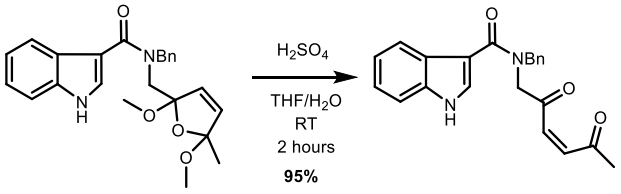
^{13}C NMR (75 MHz, $CDCl_3$) δ 169.52 (**C10**), 169.32 (**C10'**), 137.62 (**C12**), 135.88 (**C9**), 134.57 (**C20**), 131.17 (**C19**), 128.71 (**C13**/**14**), 128.64 (**C13**/**14**), 127.49 (**C2**), 127.34 (**C15**), 127.30 (**C2'**), 126.93 (**C2''**), 126.25 (**C4**), 126.02 (**C4'**), 122.35 (**C7**), 120.77 (**C6**), 120.10 (**C5**), 114.19 (**C17**), 113.15 (**C17'**), 112.04 (**C8**), 110.75 (**C3**), 110.30 (**C3'**), 110.00 (**C21**), 54.12 (**C11**), 50.47 (**C18**/**23**), 50.20 (**C18'**/**23'**), 50.15 (**C18''**/**23''**), 49.64 (**C16**), 23.61 (**C22**), 23.16 (**C22'**).

IR (cm^{-1}): 3221 (N-H stretching), 2985 (C-H stretching), 2939 (C-H stretching), 1597 (C=C stretching), 1529 (C=C aromatic stretching), 1495 (C=C aromatic stretching), 1244 (C-N stretching), 1025 (C-O stretching), 777 (C-H bending out of plan), 733 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of mono-substituted aromatic ring), 697 (C-H bending out of plan of mono-substituted aromatic ring).

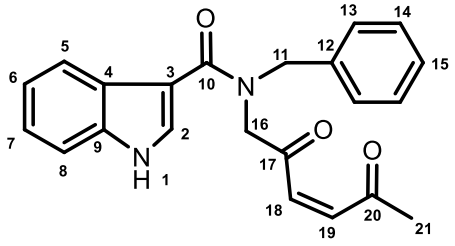
MS (FTMS +p ESI Full ms) m/z (%): 429.177 **$[M+Na]^+$** (10.1), 376.173 (22.1), 375.169 (100.0), 200.106 (13.4), 144.044 (10.9).

HRMS m/z calculated for $C_{24}H_{26}O_4N_2{}^{23}Na_1$ $[M+Na]^+$: 429.17848. Found: 429.17793.

(*Z*)-N-benzyl-N-(2,5-dioxohex-3-en-1-yl)-1H-indole-3-carboxamide



To a solution of N-benzyl-N-((2,5-dimethoxy-5-methyl-2,5-dihydrofuran-2-yl)methyl)-1H-indole-3-carboxamide (0.5 g, 1.23 mmol, 1 eq.) in tetrahydrofuran (15 ml) at room temperature was added a solution of concentrated sulfuric acid (0.01 g, 0.12 mmol, 0.1 eq., 0.005 ml) in water (5 ml). The mixture was stirred for 2 hours at room temperature then water and diethyl ether were added for extraction. The organic phases were dried over sodium sulfate and sodium hydrogencarbonate. The volatiles were removed *in vacuo* to afford the desired product as a yellow solid; 0.42 g (95%).



CAS: /

Formula: $C_{22}H_{20}N_2O_3$

Molecular weight: 360.41 g/mol

MP: 41-43°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H, **H1**), 7.97 (s, 1H, **H5**), 7.46 – 7.18 (m, 9H, **H2** + **H6** + **H7** + **H8** + **H13** + **H14** + **H15**), 6.40-6.30 (m, 2H, **H18** + **H19**), 4.91 (s, 2H, **H11**), 4.37 (s, 2H, **H16**), 2.28 (s, 3H, **H21**).

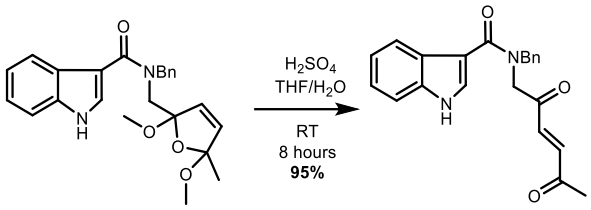
^{13}C NMR (100 MHz, $CDCl_3$) δ 200.19 (**C20**), 198.94 (**C17**), 168.95 (**C10**), 136.88 (**C12**), 135.89 (**C9**), 135.74 (**C18/19**), 135.38 (**C18/19**), 128.87 (**C14**), 127.65 (**C13**), 127.25 (**C2**), 126.66 (**C15**), 126.32 (**C4**), 122.77 (**C7**), 121.11 (**C6**), 120.57 (**C5**), 111.97 (**C8**), 109.24 (**C3**), 54.71 (**C16**), 53.81 (**C11**), 29.83 (**C21**).

IR (film, cm^{-1}): 3233 (N-H stretching), 3060 (C-H stretching), 2922 (C-H stretching), 1694 (C=O stretching), 1603 (C=C aromatic stretching + stretching of *cis* di-substituted alkene), 1576 (C=C aromatic stretching), 1527 (C=C aromatic stretching), 1495 (C=C aromatic stretching), 1454 (CH_2 scissoring), 1433 (CH_3 asymmetric deformation), 1388 (CH_3 symmetric deformation), 1244 (C-N stretching), 1191, 973, 748 (C-H bending out of plan of mono-substituted aromatic ring), 734 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of *cis* di-substituted alkene), 698 (C-H bending out of plan of mono-substituted aromatic ring).

HRMS m/z calculated for $C_{22}H_{21}N_2O_3$ $[M+H]^+$: 361.1552. Found: 361.1539. **HRMS m/z calculated for $C_{22}H_{20}N_2O_3{}^{23}Na_1$ $[M+Na]^+$:** 383.1371. Found: 383.1359.

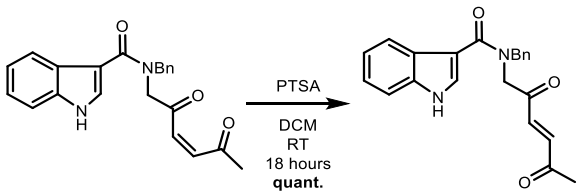
(*E*)-N-benzyl-N-(2,5-dioxohex-3-en-1-yl)-1H-indole-3-carboxamide

Methode A



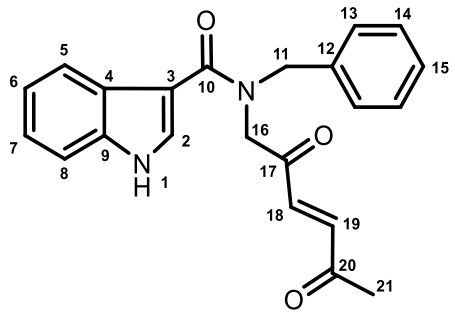
To a solution of N-benzyl-N-((2,5-dimethoxy-5-methyl-2,5-dihydrofuran-2-yl)methyl)-1H-indole-3-carboxamide (0.5 g, 1.23 mmol, 1 eq.) in tetrahydrofuran (15 ml) at room temperature was added a solution of concentrated sulfuric acid (0.01 g, 0.12 mmol, 0.1 eq., 0.005 ml) in water (5 ml). The mixture was stirred for 8 hours at room temperature then water and diethyl ether were added for extraction. The organic phases were dried over sodium sulfate and sodium hydrogencarbonate. The volatiles were removed *in vacuo* to afford the desired product as a yellow solid; 0.42 g (95%).

Methode B



To a solution of (*Z*)-N-benzyl-N-(2,5-dioxohex-3-en-1-yl)-1H-indole-3-carboxamide (0.44 g, 1.23 mmol, 1 eq.) in dichloromethane (24 ml) at room temperature was added para-toluene sulfonic acid (1 mg, 6 µmol, 0.005 eq.) and the mixture was stirred for 18 hours. The mixture was quenched by a saturated solution of sodium hydrogencarbonate in water and extracted with dichloromethane. All the organic phases were combined and dried over

sodium sulfate. The volatiles were removed *in vacuo* to afford the desired product as a slightly yellow solid; 0.44 g (quantitative).



CAS: /

Formula: $C_{22}H_{20}N_2O_3$

Molecular weight: 360.41 g/mol

MP: 39-41°C

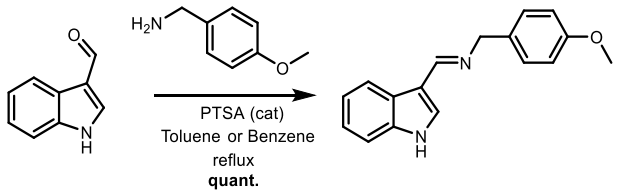
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (s, 1H, **H1**), 7.96 (d, *J* = 8.9 Hz, 1H, **H5**), 7.46 – 7.19 (m, 9H, **H2** + **H6** + **H7** + **H8** + **H13** + **H14** + **H15**), 6.87 (s, 2H, **H18** + **H19**), 4.88 (s, 2H, **H11**), 4.47 (s, 2H, **H16**), 2.33 (s, 3H, **H21**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.15 (**C20**), 195.23 (**C17**), 168.96 (**C10**), 137.46 (**C19**), 136.49 (**C12**), 135.91 (**C9**), 134.26 (**C18**), 129.04 (**C14**), 127.90 (**C13**), 127.28 (**C4**), 126.73 (**C15**), 126.27 (**C2**), 122.87 (**C7**), 121.25 (**C6**), 120.56 (**C5**), 112.00 (**C8**), 109.23 (**C3**), 54.60 (**C16**), 53.47 (**C11**), 28.21 (**C21**).

IR (film, cm^{-1}): 3247 (N-H stretching), 3060 (C-H stretching), 2923 (C-H stretching), 1685 (C=O stretching), 1600 (C=C aromatic stretching + stretching of *cis* di-substituted alkene), 1576 (C=C aromatic stretching), 1527 (C=C aromatic stretching), 1495 (C=C aromatic stretching), 1454 (CH_2 scissoring), 1433 (CH_3 asymmetric deformation), 1245 (C-N stretching), 1193, 974, 748 (C-H bending out of plan of mono-substituted aromatic ring), 735 (C-H bending out of plan of ortho di-substituted aromatic ring + C-H bending out of plan of *cis* di-substituted alkene), 698 (C-H bending out of plan of mono-substituted aromatic ring).

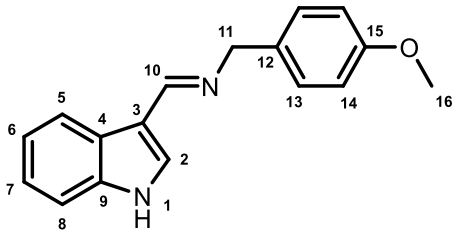
HRMS m/z calculated for $C_{22}H_{21}N_2O_3$ $[M+H]^+$: 361.1552. Found: 361.1542. **HRMS m/z calculated for $C_{22}H_{20}N_2O_3{}^{23}Na_1$ $[M+Na]^+$:** 383.1371. Found: 383.1364.

1-(1H-indol-3-yl)-N-(4-methoxybenzyl)methanimine



To a solution of 1H-indole-3-carbaldehyde (40 g, 0.275 mol, 1 eq.) and PTSA (0.24 g, 0.0014 mol, 0.005 eq.) in toluene (350 ml) or benzene (350 ml) was added *p*-methoxy-benzylamine (39.69 g, 0.289 mol, 1.05 eq., 37.8 ml). The resulting mixture was refluxed with a Dean-Stark apparatus until the correct amount of water (5 ml) was retrieved. The solvent was removed at low pressure to afford a yellow-orange solid; 72.8 g (quantitative).

This solid was directly used without more purification.



CAS: 86427-28-3

Formula: $C_{17}H_{16}N_2O_1$

Molecular weight: 264.34 g/mol

MP: 85-89°C **Litt[7]:** 162°C

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H, **H10**), 8.40 – 8.30 (m, 1H, **H5**), 7.48 (s, 1H, **H5**), 7.37 – 7.26 (m, 3H, **H8** + **H13**), 7.26 – 7.17 (m, 2H, **H6** + **H7**), 6.92 – 6.85 (m, 2H, **H14**), 4.77 (s, 2H, **H11**), 3.80 (s, 3H, **H16**).

^{13}C NMR (75 MHz, $CDCl_3$) δ 158.60 (**C15**), 156.17 (**C10**), 136.84 (**C9**), 132.65 (**C12**), 129.11 (**C13**), 128.62 (**C2**), 125.62 (**C4**), 123.40 (**C7**), 121.94 (**C5**), 121.48 (**C6**), 115.84 (**C3**), 113.96 (**C14**), 111.35 (**C8**), 65.01 (**C11**), 55.44 (**C16**).

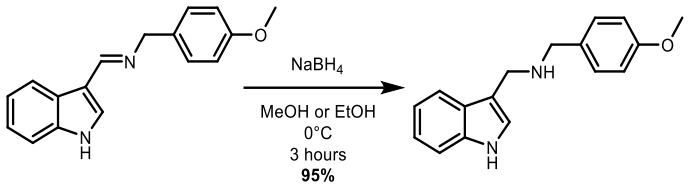
[7] Kumar, P.; Nath, C.; Bhargava, K. P.; Shanker, K. *Indian J. Chem. B*, **1982**, *21*, 1128.

IR (film, cm^{-1}): 3398 (N-H stretching), 3057 (C-H stretching), 3004 (C-H stretching), 2955 (C-H stretching), 2929 (C-H stretching), 2833 (C-H stretching), 1629 (C=N stretching), 1608 (C=C aromatic stretching), 1577 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1439 (CH_2 scissoring), 1239 (C-N stretching), 1172 (C-O stretching), 1027 (C-O stretching), 818 (C-H bending out of plan of para disubstituted aromatic ring), 733 (C-H bending out of plan of para disubstituted aromatic ring).

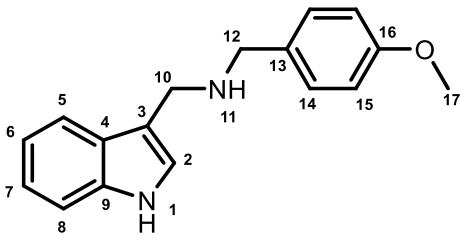
MS (FTMS +p ESI Full ms2) m/z (%): 265.132 $[M+H]^+$ (25.0), 121.064 (100.0).

HRMS m/z calculated for $C_{17}H_{17}O_1N_2$ $[M+H]^+$: 265.13354. Found: 265.13342.

N-((1H-indol-3-yl)methyl)-1-(4-methoxyphenyl)methanamine



1-(1H-indol-3-yl)-N-(4-methoxybenzyl)methanimine (72.8 g, 0.275 mol, 1 eq.) was dissolved in methanol (300 ml) or ethanol (300 ml) at 0°C. Then $NaBH_4$ (22.9 g, 0.60 mol, 2.2 eq.) was added portionwise and the temperature was kept below 10°C. The mixture was stirred at 0°C for 3 hours then 25-35% aqueous ammonia solution was added (300 ml) and the biphasic mixture was stirred for 2 hours. The solvent was slowly eliminated under vacuum. The resulting aqueous phase was extracted 3 time with dichloromethane, the organic layers were combined and dried over Na_2SO_4. The solvent was eliminated under low pressure providing a yellow solid which can be precipitated with diethyl ether and pentane to a white solid; 69.7 g (95%).



CAS: /

Formula: $C_{17}H_{18}N_2O_1$

Molecular weight: 266.34 g/mol

MP: 77-79°C **Litt[8]:** 89°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H, **H1**), 7.65 (d, *J* = 7.8 Hz, 1H, **H5**), 7.38 – 7.31 (m, 1H, **H8**), 7.31 – 7.25 (m, 2H, **H14**), 7.23 – 7.16 (m, 1H, **H7**), 7.16 – 7.08 (m, 2H, **H2** + **H6**), 6.93 – 6.83 (m, 2H, **H15**), 3.99 (s, 2H, **H10**), 3.82 (s, 2H, **H12**), 3.80 (s, 3H, **H17**), 1.57 (s, 1H, **H11**).

[8] Turet, L.; Markó, I. E.; Tinant, B.; Declercq, J-P.; Touillaux, R. *Tetrahedron lett*., **2002**, *43*, 6591.

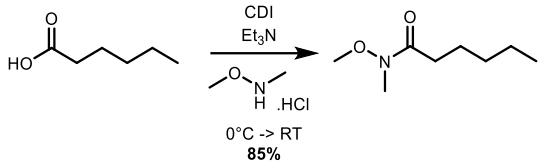
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.55 (**C16**), 136.30 (**C9**), 131.69 (**C13**), 129.43 (**C14**), 126.89 (**C4**), 123.22 (**C2**), 121.67 (**C7**), 119.14 (**C6**), 118.44 (**C5**), 113.75 (**C15**), 113.35 (**C3**), 111.41 (**C8**), 55.04 (**C17**), 52.45 (**C12**), 43.66 (**C10**).

IR (cm^{-1}): 3410 (N-H stretching) 3159 (N-H stretching), 2911 (C-H stretching), 2833 (C-H stretching), 1610 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1454 (CH_2 scissoring), 1243 (C-N stretching), 1176 (C-O stretching), 1031 (C-O stretching), 813 (C-H bending out of plan of para disubstituted aromatic ring), 741 (C-H bending out of plan of ortho disubstituted aromatic ring).

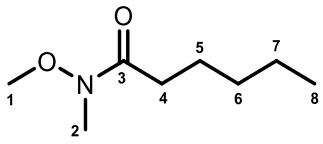
MS (FTMS +p ESI Full ms2) m/z (%): 267.148 $[M+H]^+$ (5.0), 130.064 (100.0), 121.064 (17.0).

HRMS m/z calculated for $C_{17}H_{19}O_1N_2$ $[M+H]^+$: 267.14919. Found: 267.14894.

N-methoxy-N-methylhexanamide



Hexanoic acid (27.1 g, 0.233 mmol, 1 eq., 29.1 ml) is dissolved in dichloromethane (500 ml) at 0°C then 1,1'-carbonyldiimidazole (41.6 g, 0.256 mmol, 1.1 eq.) is added portionwise at 0°C. When no more gas is produced, triethylamine (25.9 g, 0.256 mmol, 1.1 eq., 34.6 ml) is added followed by N, O-dimethyl-hydroxylamine (25 g, 0.256 mmol, 1.1 eq.) at 0°C. The final mixture is stirred at room temperature for 2 hours then a three-molar solution of aqueous hydrochloric acid is added as quench and the mixture is extracted with diethyl ether. The organic phases are combined and dried over sodium sulfate, the volatiles are removed *in vacuo* to afford a slightly yellow oil. This oil was distilled under vacuum to afford the desired product as a colourless oil; 31.5 g (85%).



CAS: 64214-56-8

Formula: $C_8H_{17}NO_2$

Molecular weight: 159.22 g/mol

BP: 100-102°C at 12 torrs **Litt:** /

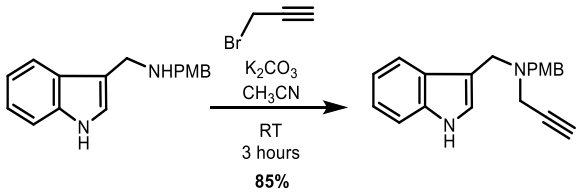
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.68 (s, 3H, **H1**), 3.18 (s, 3H, **H2**), 2.41 (t, *J* = 7.6 Hz, 2H, **H4**), 1.71 – 1.57 (m, 2H, **H5**), 1.41 – 1.26 (m, 4H, **H6** + **H7**), 0.90 (t, *J* = 6.9 Hz, 3H, **H8**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 174.76 (**C3**), 61.12 (**C1**), 32.08 (**C2**), 31.80 (**C4**), 31.56 (**C6**), 24.28 (**C5**), 22.42 (**C7**), 13.88 (**C8**).

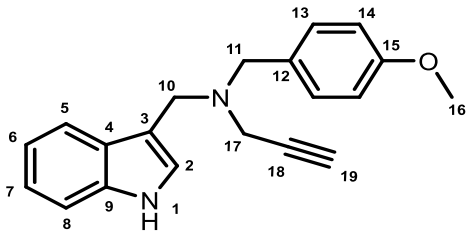
IR (film, cm^{-1}): 2956 (C-H stretching), 2933 (C-H stretching), 2872 (C-H stretching), 1661 (C=O stretching from tertiary amide), 1467 (CH_2 scissoring), 1413 (CH_3 asymmetric deformation), 1382 (CH_3 asymmetric deformation), 1176 (C-O stretching + C-N stretching), 1002 (N-O stretching).

The compound was already described in the literature:
Lee, N. R.; Lee, J. I. *Synth. Comm*., **1999**, *29*, 1249.

N-((1H-indol-3-yl)methyl)-N-(4-methoxybenzyl)prop-2-yn-1-amine



N-((1H-indol-3-yl)methyl)-1-(4-methoxyphenyl)methanamine (20 g, 75 mmol, 1 eq.) and potassium carbonate (31 g, 225 mmol, 3 eq.) were suspended in stirring acetonitrile (400) at room temperature. Then propargyl bromide (80% in toluene) (82.6 mmol, 1.1 eq., 9.2 ml) was drop wisely added and the resulting mixture was stirred for 3 hours at room temperature. Water was added, and the solution was extracted three time with dichloromethane, the organic phases were combined, and the volatiles were removed *in vacuo* to afford a yellow oil. This oil was suspended in diethyl ether, a precipitate was formed and filtered. The solvent was removed under vacuum to afford a yellow solid. This solid was suspended in pentane then diethyl ether was added, and the mixture was stirred during 8 hours at room temperature. A white solid was filtered off and dried under vacuum to afford the desired compound as an off-white solid; 19.4 g (85%).



CAS: /

Formula: $C_{20}H_{20}N_2O$

Molecular weight: 304.39 g/mol

MP: 96-97°C **Litt:** /

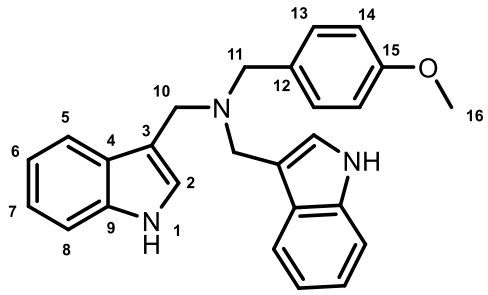
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H, **H1**), 7.76 (d, *J* = 7.7 Hz, 1H, **H5**), 7.30 (d, *J* = 8.6 Hz, 2H, **H13**), 7.25 (d, *J* = 7.8 Hz, 1H, **H8**), 7.16 (td, *J* = 7.4, 1.0 Hz, 1H, **H7**), 7.13 – 7.08 (m, 1H, **H6**), 7.05 (d, *J* = 2.2 Hz, 1H, **H2**), 6.84 (d, *J* = 8.6 Hz, 2H, **H14**), 3.85 (s, 2H, **H10**), 3.75 (s, 3H, **H16**), 3.66 (s, 2H, **H11**), 3.25 (d, *J* = 2.3 Hz, 2H, **H17**), 2.27 (t, *J* = 2.3 Hz, 1H, **H19**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.77 (**C15**), 136.49 (**C9**), 131.13 (**C12**), 130.38 (**C13**), 127.78 (**C4**), 123.91 (**C2**), 122.10 (**C7**), 119.83 (**C5**), 119.52 (**C6**), 113.76 (**C14**), 113.07 (**C3**), 111.16 (**C8**), 79.03 (**C18**), 73.49 (**C19**), 56.95 (**C11**), 55.31 (**C16**), 48.58 (**C10**), 40.82 (**C7**).

IR (film, cm^{-1}): 3413 (N-H stretching), 3287 (C-H stretching from triple bond), 2920 (C-H stretching), 2832 (C-H stretching), 1610 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1454 (CH_2 scissoring), 1243 (C-N stretching), 1032 (C-O stretching), 809 (C-H bending out of plan of para disubstituted aromatic ring), 740 (C-H bending out of plan of ortho disubstituted aromatic ring), 636 (C-H bending out of plan of terminus alkynes).

HRMS m/z calculated for $C_{20}H_{21}N_2O_1$ $[M+H]^+$: 305.1653. Found: 305.1651.
HRMS m/z calculated for $C_{20}H_{20}N_2O_1{}^{23}Na_1$ $[M+Na]^+$: 327.1473. Found: 327.1477.

N,N-bis((1H-indol-3-yl)methyl)-1-(4-methoxyphenyl)methanamine



CAS: /

Formula: $C_{26}H_{25}N_3O$

Molecular weight: 395.50 g/mol

Off-white solid

MP: 45-52°C **Litt:** /

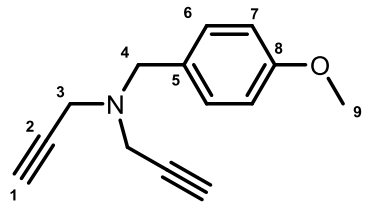
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (s, 2H, **H1**), 7.67 (d, *J* = 7.8 Hz, 2H, **H5**), 7.34 (dt, *J* = 8.2, 0.8 Hz, 2H, **H8**), 7.32 – 7.28 (m, 2H, **H13**), 7.20 – 7.13 (m, 4H, **H2** + **H7**), 7.08 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 2H, **H6**), 6.88 – 6.81 (m, 2H, **H14**), 3.79 (s, *J* = 6.9 Hz, 7H, **H10** + **H16**), 3.57 (s, 2H, **H11**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.47 (**C15**), 136.49 (**C9**), 132.42 (**C12**), 130.27 (**C13**), 127.95 (**C4**), 123.57 (**C2**), 121.95 (**C7**), 120.10 (**C5**), 119.31 (**C6**), 114.08 (**C3**), 113.61 (**C14**), 111.05 (**C8**), 57.50 (**C11**), 55.35 (**C16**), 49.15 (**C10**).

IR (film, cm^{-1}): 3411 (N-H stretching), 3054 (C-H stretching), 2930 (C-H stretching), 2791 (C-H stretching), 1610 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1454 (CH_2 scissoring), 1238 (C-N stretching), 1031 (C-O stretching), 817 (C-H bending out of plan of para disubstituted aromatic ring, 739 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{26}H_{26}N_3O$ $[M+H]^+$: 396.2075. Found: 396.2067.
HRMS m/z calculated for $C_{26}H_{25}N_3O^{23}Na_1$ $[M+Na]^+$: 418.1895. Found: 418.1903.

N-(4-methoxybenzyl)-N-(prop-2-yn-1-yl)prop-2-yn-1-amine



CAS: /

Formula: $C_{14}H_{15}NO$

Molecular weight: 213.28 g/mol

Colourless oil

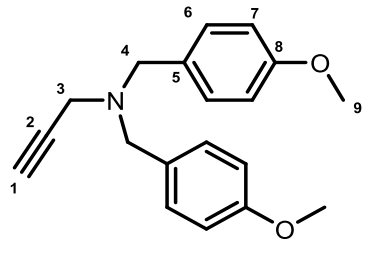
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H, **H6**), 6.89 – 6.82 (m, 2H, **H7**), 3.80 (s, 3H, **H9**), 3.62 (s, 2H, **H4**), 3.40 (d, *J* = 2.4 Hz, 4H, **H3**), 2.26 (t, *J* = 2.4 Hz, 2H, **H1**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.03 (**C8**), 130.46 (**C6**), 129.75 (**C5**), 113.81 (**C7**), 78.96 (**C2**), 73.27 (**C1**), 56.50 (**C4**), 55.26 (**C9**), 41.68 (**C3**).

IR (film, cm^{-1}): 3289 (C-H stretching from terminus alkyne), 2932 (C-H stretching), 2833 (C-H stretching), 1611 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1243 (C-N stretching), 1172 (C-O stretching), 1033 (C-O stretching), 809 (C-H bending out of plan of para disubstituted aromatic ring), 635 (C-H bending out of plan of terminus alkyne).

HRMS m/z calculated for $C_{14}H_{16}N_1O_1$ $[M+H]^+$: 214.1231. Found: 214.1230.

N,N-bis(4-methoxybenzyl)prop-2-yn-1-amine



CAS: /

Formula: $C_{19}H_{21}NO_2$

Molecular weight: 295.38 g/mol

Colourless oil

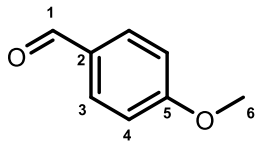
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 4H, **H8**), 6.89 – 6.82 (m, 4H, **H7**), 3.79 (s, 6H, **H9**), 3.60 (s, 4H, **H4**), 3.22 (d, *J* = 2.4 Hz, 2H, **H3**), 2.26 (t, *J* = 2.4 Hz, 1H, **H1**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.79 (**C8**), 130.90 (**C5**), 130.21 (**C6**), 113.72 (**C7**), 78.72 (**C2**), 73.39 (**C1**), 56.69 (**C4**), 55.26 (**C9**), 40.81 (**C3**).

IR (film, cm^{-1}): 3290 (C-H stretching from terminus alkyne), 2932 (C-H stretching), 2834 (C-H stretching), 1612 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1244 (C-N stretching), 1173 (C-O stretching), 1034 (C-O stretching), 809 (C-H bending out of plan of para disubstituted aromatic ring), 635 (C-H bending out of plan of terminus alkyne).

HRMS m/z calculated for $C_{19}H_{22}N_1O_2$ $[M+H]^+$: 296.1650. Found: 296.1648. **HRMS m/z calculated for $C_{19}H_{21}N_1O_2{}^{23}Na_1$ $[M+Na]^+$:** 318.1469. Found: 318.1451.

4-methoxybenzaldehyde



CAS: 123-11-5

Formula: $C8H8O_2$

Molecular weight: 136.15 g/mol

Colourless oil

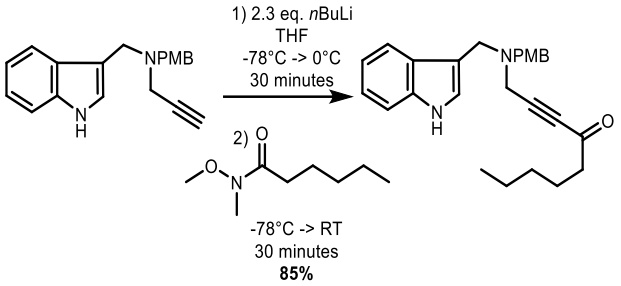
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.88 (s, 1H, **H1**), 7.87 – 7.79 (m, 2H, **H3**), 7.03 – 6.96 (m, 2H, **H4**), 3.89 (s, 3H, **H6**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 190.75 (**C1**), 164.58 (**C5**), 131.91 (**C3**), 129.90 (**C2**), 114.28 (**C4**), 55.52 (**C6**).

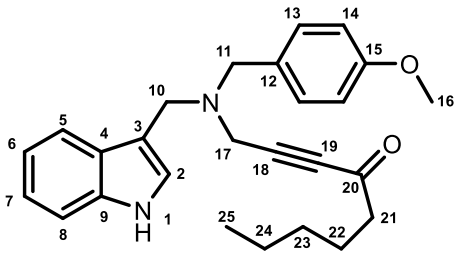
IR (film, cm^{-1}): 2840 (C-H stretching), 2739 (C-H stretching), 1678 (C=O stretching), 1594 (C=C aromatic stretching), 1575 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1155 (C-O stretching), 1020 (C-O stretching), 827 (C-H bending out of plan of para disubstituted aromatic ring.

The compound was already described in the literature:
Cahours, v. A. *Justus Liebigs Annalen der Chemie*, **1842**, *41*, 65.

1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)non-2-yn-4-one



To a solution of N-((1H-indol-3-yl)methyl)-N-(4-methoxybenzyl)prop-2-yn-1-amine (12 g, 39.4 mmol, 1 eq.) in anhydrous tetrahydrofuran (240 ml) at -78°C was added *n*-butyllithium 2.5M in hexane (91 mmol, 2.3 eq., 36.3 ml) in 2 minutes. The acetone/dry ice bath was removed to a water/ice bath for 30 minutes. The mixture was cooled to -78°C again and N-methoxy-N-methylhexanamide (8.2 g, 51.2 mmol, 1.3 eq., 8.8 ml) was added neat. The acetone/dry ice bath was removed, and the reaction was stirred for 30 minutes. The solution was purred on diethyl ether and 5M aqueous solution of ammonium chloride, the aqueous phase was extracted once with diethyl ether. The ether phases were combined and dried over sodium sulfate then the volatiles were removed in vacuum to provide a yellow-orange oil. This oil was dissolvent in acetonitrile (10 ml for 1 g of N-((1H-indol-3-yl)methyl)-N-(4-methoxybenzyl)prop-2-yn-1-amine starting material) and the acetonitrile phase was washed 6 times with hexane (5 ml for 1 g of N-((1H-indol-3-yl)methyl)-N-(4-methoxybenzyl)prop-2-yn-1-amine). The acetonitrile was dried again on sodium sulfate and the volatiles were removed *in vacuo* to afford the desired product as a yellow oil; 13.5 g (85%).



CAS: /

Formula: $C_{26}H_{30}N_2O_2$

Molecular weight: 402.53 g/mol

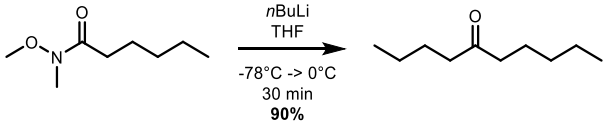
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (s, 1H, **H1**), 7.76 (d, *J* = 7.4 Hz, 1H, **H5**), 7.39 – 7.33 (m, 1H, **H8**), 7.33 – 7.27 (m, 2H, **H13**), 7.24 – 7.18 (m, 1H, **H7**), 7.17 – 7.09 (m, 2H, **H2** + **H6**), 6.89 – 6.84 (m, 2H, **H14**), 3.89 (s, 2H, **H10**), 3.80 (s, 3H, **H16**), 3.69 (s, 2H, **H11**), 3.42 (s, 2H, **H17**), 2.60 (t, *J* = 7.5 Hz, 2H, **H21**), 1.82 – 1.70 (m, 2H, **H22**), 1.44 – 1.28 (m, 4H, **H23** + **H24**), 0.92 (t, *J* = 7.0 Hz, 3H, **H25**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.38 (**C20**), 158.72 (**C15**), 136.51 (**C9**), 130.42 (**C12**), 130.11 (**C13**), 127.44 (**C4**), 124.01 (**C2**), 121.84 (**C7**), 119.46 (**C5**), 119.22 (**C6**), 113.65 (**C14**), 112.05 (**C3**), 111.23 (**C8**), 89.15 (**C19**), 85.30 (**C18**), 57.10 (**C11**), 55.04 (**C16**), 48.93 (**C10**), 45.60 (**C21**), 40.75 (**C17**), 31.04 (**C23**), 23.88 (**C22**), 22.33 (**C24**), 13.85 (**C25**).

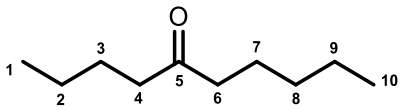
IR (film, cm^{-1}): 3408 (N-H stretching), 2954 (C-H stretching), 2929 (C-H stretching), 2204 (C≡C stretching), 1665 (C=O stretching), 1611 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1455 (CH_2 scissoring), 1244 (C-N stretching), 811 (C-H bending out of plan of para disubstituted aromatic ring), 740 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{26}H_{31}N_2O_2$ $[M+H]^+$: 403.2385. Found: 403.2373.

decan-5-one



To a solution of N-methoxy-N-methylhexanamide (0.46 g, 2.9 mmol, 1 eq., 0.5 ml) in tetrahydrofuran (20 ml) at -78°C was added drop wisely *n*-Butyl Lithium 2.5 Molar in hexane (3.8 mmol, 1.3 eq., 1.5 ml). At the end of the addition the mixture was allowed to evolve to 0°C over 30 minutes, then it was quenched by dropwise addition of a saturated aqueous solution of ammonium chloride. The biphasic mixture was extracted with diethyl ether, the organic phases were combined and dried over sodium sulfate. The volatiles were removed without vacuum to afford the desired product as a colourless oil; 0.4 g (90%).



CAS: 820-29-1

Formula: $C_{10}H_{20}O_1$

Molecular weight: 156.27 g/mol

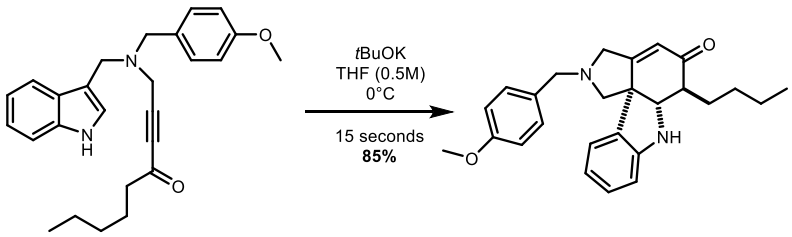
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (t, *J* = 7.5 Hz, 2H, **H4/6**), 2.37 (t, *J* = 7.5 Hz, 2H, **H4/6**), 1.61 – 1.49 (m, 4H, **H3** + **H7**), 1.37 – 1.19 (m, 6H, **H2** + **H8** + **H9**), 0.89 (t, *J* = 7.3 Hz, 3H, **H1/10**), 0.90 – 0.85 (m, 3H, **H1/H10**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.79 (**C5**), 42.86 (**C6**), 42.61 (**C4**), 31.54 (**C8**), 26.08 (**C3**), 23.66 (**C7**), 22.56 (**C9**), 22.47 (**C2**), 14.00 (**C10**), 13.94 (**C1**).

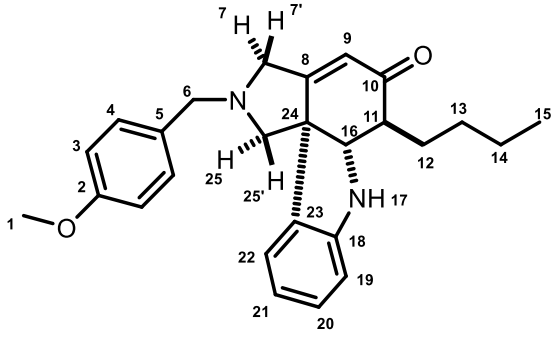
IR (cm^{-1}): 3956 (C-H stretching), 2931 (C-H stretching), 2872 (C-H stretching), 1712 (C=O stretching of acyclic saturated ketone), 1464 (CH_2 scissoring), 1410 (CH_3 asymmetric deformation), 1377 (CH_3 symmetric deformation), 1132 (C-C stretching), 1048 (C-C stretching), 748 (CH_2 rocking), 731 (CH_2 rocking).

The compound was already described in the literature:
Church, J. M.; Whitmore, F. C.; McGrew R. V. *J. Am. Chem. Soc.*, **1934**, *56*, 176.

(6S,6aS,11bS)-6-butyl-2-(4-methoxybenzyl)-2,3,6a,7-tetrahydro-1H-pyrrolo[3,4-d]carbazol-5(6H)-one



To a solution of ynone (8.5 g, 21.1 mmol, 1eq.) in anhydrous tetrahydrofuran (42 ml) at 0°C was added solid potassium *tert*-butoxide (0.24 g, 2.1 mmol, 0.1 eq.). After 15 seconds of reaction, the mixture is purred on diethyl ether and 5M ammonium chloride aqueous solution and shook vigorously. The aqueous phase was extracted with diethyl ether. All the ether phases were combined and dried over sodium sulfate. The volatiles were removed *in vacuo* leading to a brownish oil which can be purified by column chromatography using flash silica gel, petroleum ether and diethyl ether to afford the product as a yellow solid; 7.22 g (85%).



CAS: /

Formula: $C_{26}H_{30}N_2O_2$

Molecular weight: 402.53 g/mol

MP: 36-39°C **Litt:** /

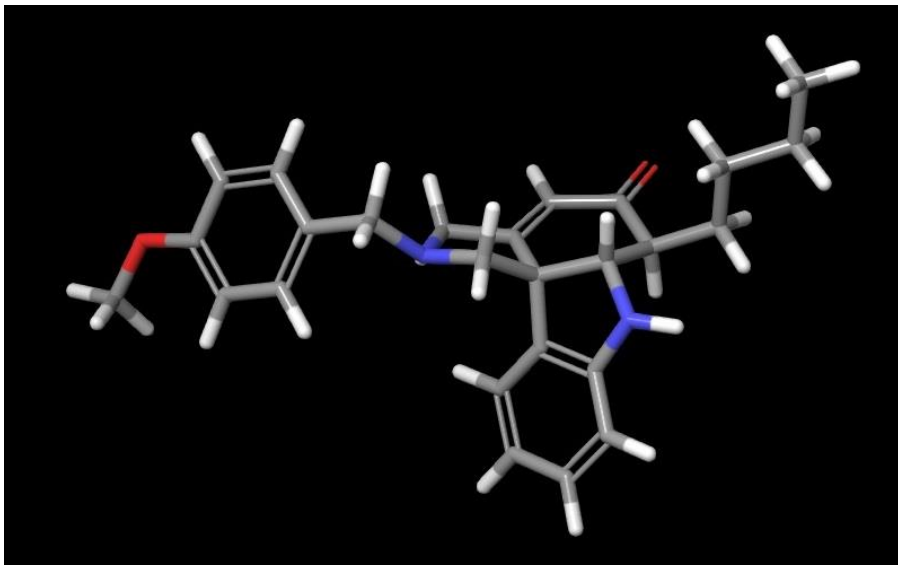
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.25 (m, 1H, **H22**), 7.23 (d, *J* = 8.6 Hz, 2H, **H4**), 7.13 (td, *J* = 7.6, 1.3 Hz, 1H, **H20**), 6.87 – 6.81 (m, 3H, **H3** + **H21**), 6.72 (d, *J* = 7.6 Hz, 1H, **H19**), 5.92 (t, *J* = 1.6 Hz, 1H, **H9**), 4.13 – 4.04 (bs, 1H, **H17**), 4.09 (dd, *J* = 17.4, 1.8 Hz, 1H, **H7**), 3.80 (d, *J* = 12.9 Hz, 1H, **H6**), 3.80

(s, 3H, **H1**), 3.79 (d, *J* = 9.5 Hz, 1H, **H16**), 3.56 (d, *J* = 13.0 Hz, 1H, **H6'**), 3.20 (d, *J* = 17.6 Hz, 1H, **H7'**), 3.09 (d, *J* = 8.0 Hz, 1H, **H25**), 2.58 (d, *J* = 8.1 Hz, 1H, **H25'**), 2.33 (dt, *J* = 9.6, 4.8 Hz, 1H, **H11**), 1.75 – 1.61 (m, 2H, **H12**), 1.46 – 1.15 (m, 4H, **H13** + **H14**), 0.91 (t, *J* = 7.1 Hz, 3H, **H15**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 198.62 (**C10**), 164.12 (**C8**), 158.87 (**C2**), 148.34 (**C18**), 132.36 (**C23**), 130.64 (**C5**), 129.67 (**C4**), 128.62 (**C20**), 124.82 (**C22**), 122.39 (**C9**), 119.60 (**C21**), 113.89 (**C3**), 110.59 (**C19**), 67.17 (**C16**), 65.69 (**C25**), 58.81 (**C6**), 56.86 (**C7**), 55.72 (**C24**), 55.38 (**C1**), 48.40 (**C11**), 29.14 (**C13**), 26.72 (**C12**), 23.27 (**C14**), 14.13 (**C15**).

IR (film, cm^{-1}): 3363 (N-H stretching), 2954 (C-H stretching), 2930 (C-H stretching), 1665 (C=O stretching from α,β unsaturated ketone in a 6 membered ring), 1606 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1463 (CH_2 scissoring), 1247 (C-N stretching), 1033 (C-O stretching), 819 (C-H bending out of plan of para disubstituted aromatic ring + C-H bending out of plan of trisubstituted alkene), 745 (C-H bending out of plan of ortho disubstituted aromatic ring).

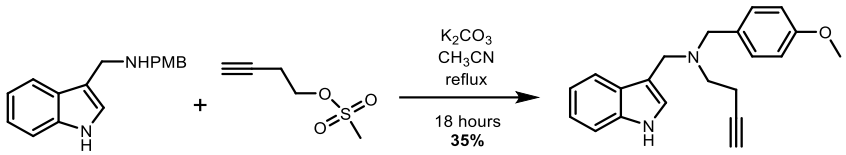
HRMS m/z calculated for $C_{26}H_{31}N_2O_2$ $[M+H]^+$: 403.2385. Found: 403.2369. **HRMS m/z calculated for $C_{26}H_{30}N_2O_2{}^{23}Na_1$ $[M+Na]^+$:** 425.2204. Found: 425.2192.



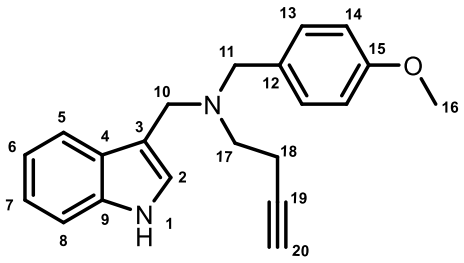
Final report; processing .tmp file:
169 unique conformations found so far
169 minimized with good convergence
Found 7 confs within 1.00 kcal/mol (4.18 kJ/mol) of glob. min.
Found 26 confs within 2.00 kcal/mol (8.37 kJ/mol) of glob. min.
Found 57 confs within 3.00 kcal/mol (12.55 kJ/mol) of glob. min.
Found 168 confs within 5.00 kcal/mol (20.92 kJ/mol) of glob. min.
Found 169 confs within 10.00 kcal/mol (41.84 kJ/mol) of glob. min.
Global minimum E = 386.23 found 5 times.
1000 steps performed so far, out of 1000
E of low-energy structures above global min [kJ/mol], and no. times found:
E: 0.00 0.95 1.22 2.16 2.97 3.30 4.04 4.49 4.51 4.53 4.78 4.95
No.: 5 3 12 12 4 4 5 3 7 7 3 8

Input structure with title on the next line is given SerNo: 1
O=C1[C@@H](CCCC)[C@@H]([C@@]23C(CN(CC4=CC=C(OC)C=C4)C3)=C1)NC5=C2C=CC=C5
Auto summary for input structure 1:
Total number of structures processed = 1000
Conformations with poor convergence marked with a *
Conformation 1 (386.2272 kJ/mol) was found 5 times
Conformation 2 (387.1737 kJ/mol) was found 3 times
Conformation 3 (387.4503 kJ/mol) was found 12 times
Conformation 4 (388.3887 kJ/mol) was found 12 times
Conformation 5 (389.1987 kJ/mol) was found 4 times
Conformation 6 (389.5239 kJ/mol) was found 4 times
Conformation 7 (390.2685 kJ/mol) was found 5 times
Conformation 8 (390.7177 kJ/mol) was found 3 times
Conformation 9 (390.7361 kJ/mol) was found 7 times
Conformation 10 (390.7552 kJ/mol) was found 7 times
Conformation 11 (391.0072 kJ/mol) was found 3 times
Conformation 12 (391.1813 kJ/mol) was found 8 times
Conformation 13 (391.2146 kJ/mol) was found 6 times
Conformation 14 (391.6545 kJ/mol) was found 5 times
Conformation 15 (391.6986 kJ/mol) was found 6 times

N-((1H-indol-3-yl)methyl)-N-(4-methoxybenzyl)but-3-yn-1-amine



To a solution of N-((1H-indol-3-yl)methyl)-1-(4-methoxyphenyl)methanamine (3.6 g, 13.5 mmol, 1 eq.) and potassium carbonate (5.9 g, 42.7 mmol, 3 eq.) in anhydrous acetonitrile (70 ml) was added but-3-yn-1-yl methanesulfonate (2.1 g, 14.2 mmol, 1.05 eq.) and the reaction was stirred at reflux for 18 hours. The mixture was cooled to room temperature and extracted with water and diethyl ether, the organic phases were combined and dried over sodium sulfate, finally the volatiles were removed *in vacuo* to furnish a yellow/orange oil. This oil was solubilised in diethyl ether and the precipitate was filtered. The ether phase was recovered, and the solvent was removed *in vacuo* to afford a yellow oil. This oil was purified by column chromatography using flash silica gel, dichloromethane and methanol to afford the desired product as a pale-yellow oil; 1.5 g (35%).



CAS: /

Formula: $C_{21}H_{22}N_2O$

Molecular weight: 318.42 g/mol

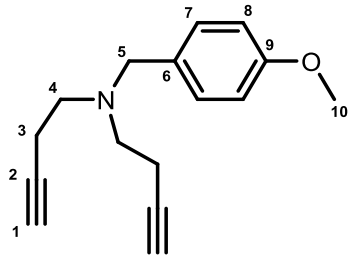
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (bs, 1H, **H1**), 7.75 (d, *J* = 7.9 Hz, 1H, **H5**), 7.40 – 7.31 (m, 1H, **H8**), 7.27 (d, *J* = 8.4 Hz, 2H, **H13**), 7.19 (t, *J* = 7.4 Hz, 1H, **H6**), 7.16 – 7.09 (m, 2H, **H2** + **H7**), 6.84 (d, *J* = 8.4 Hz, 2H, **H14**), 3.81 (s, 2H, **H10**), 3.79 (s, 3H, **H16**), 3.59 (s, 2H, **H11**), 2.72 (t, *J* = 7.5 Hz, 2H, **H17**), 2.38 (td, *J* = 7.5, 2.6 Hz, 2H, **H18**), 1.92 (dt, *J* = 2.7, 1.3 Hz, 1H, **H20**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.61 (**C15**), 136.55 (**C9**), 131.82 (**C12**), 130.06 (**C13**), 127.76 (**C4**), 123.45 (**C7**), 122.08 (**C2**), 120.00 (**C5**), 119.42 (**C6**), 113.67 (**C14**), 113.63 (**C3**), 111.09 (**C8**), 83.53 (**C19**), 69.06 (**C20**), 57.59 (**C11**), 55.32 (**C16**), 51.99 (**C17**), 49.41 (**C10**), 17.12 (**C18**).

IR (film, cm^{-1}): 3415 (N-H stretching), 3290 (C-H stretching from triple bond), 2930 (C-H stretching), 2833 (C-H stretching), 1610 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1454 (CH_2 scissoring), 1237 (C-N stretching), 1072 (C-O stretching), 1030 (C-O stretching), 814 (C-H bending out of plan of para disubstituted aromatic ring), 739 (C-H bending out of plan of ortho disubstituted aromatic ring), 635 (C-H bending out of plan of terminus alkynes).

HRMS m/z calculated for $C_{21}H_{23}N_2O_1$ $[M+H]^+$: 319.1810. Found: 319.1809
HRMS m/z calculated for $C_{21}H_{22}N_2O_1{}^{23}Na_1$ $[M+Na]^+$: 341.1629. Found: 341.1636.

N-(but-3-yn-1-yl)-N-(4-methoxybenzyl)but-3-yn-1-amine



CAS: /

Formula: $C_{16}H_{19}NO$

Molecular weight: 241.33 g/mol

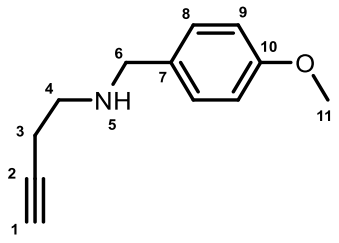
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.8 Hz, 2H, **H7**), 6.88 – 6.81 (m, 2H, **H8**), 3.80 (s, *J* = 2.2 Hz, 3H, **H10**), 3.60 (s, 2H, **H5**), 2.73 (t, *J* = 7.4 Hz, 4H, **H4**), 2.33 (td, *J* = 7.4, 2.7 Hz, 4H, **H3**), 1.95 (t, *J* = 2.7 Hz, 2H, **H1**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.72 (**C9**), 131.12 (**C6**), 129.80 (**C7**), 113.68 (**C8**), 82.94 (**C2**), 69.04 (**C1**), 57.60 (**C5**), 55.26 (**C10**), 52.24 (**C4**), 17.28 (**C3**).

IR (film, cm^{-1}): 3291 (C-H stretching terminus triple bond), 2953 (C-H stretching), 2914 (C-H stretching), 2834 (C-H stretching), 1610 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1460 (CH_2 scissoring), 1241 (C-N stretching), 1171 (C-O stretching), 1033 (C-O stretching), 816 (C-H bending out of plan of para disubstituted aromatic ring), 633 (C-H bending out of plan of terminus alkyne).

HRMS m/z calculated for $C_{16}H_{20}N_1O_1$ $[M+H]^+$: 242.1544. Found: 242.1531. **HRMS m/z calculated for $C_{16}H_{19}N_1O_1{}^{23}Na_1$ $[M+Na]^+$:** 264.1364. Found: 264.1340.

N-(4-methoxybenzyl)but-3-yn-1-amine



CAS: 146980-79-2

Formula: $C_{12}H_{15}N_1O_1$

Molecular weight: 189.25 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.22 (m, 2H, **H8**), 6.89 – 6.84 (m, 2H, **H9**), 3.80 (s, 3H, **H11**), 3.76 (s, 2H, **H6**), 2.79 (t, *J* = 6.6 Hz, 2H, **H4**), 2.41 (td, *J* = 6.6, 2.7 Hz, 2H, **H3**), 1.99 (t, *J* = 2.7 Hz, 1H, **H1**), 1.58 (s, 1H, **H5**).

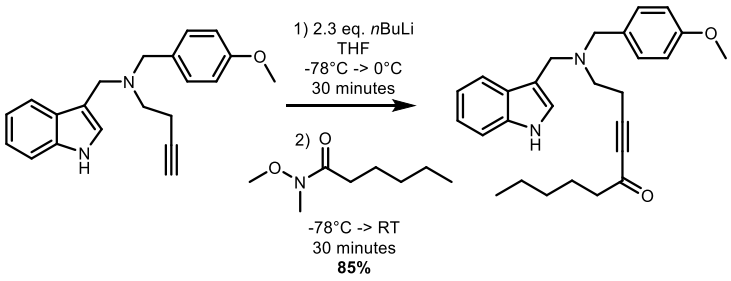
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.78 (**C10**), 132.30 (**C7**), 129.40 (**C8**), 113.93 (**C9**), 82.61 (**C2**), 69.65 (**C1**), 55.37 (**C11**), 52.85 (**C6**), 47.30 (**C4**), 19.61 (**C3**).

IR (film, cm^{-1}): 3289 (C-H stretching terminus triple bond), 2941 (C-H stretching), 2834 (C-H stretching), 1611 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1455 (CH_2 scissoring), 1241 (C-N stretching), 1175 (C-O stretching), 1032 (C-O stretching), 811 (C-H bending out of plan of para disubstituted aromatic ring), 634 (C-H bending out of plan of terminus alkyne).

HRMS m/z calculated for $C_{12}H_{16}N_1O_1$ $[M+H]^+$: 190.1231. Found: 190.1228.
HRMS m/z calculated for $C_{12}H_{15}N_1O_1{}^{23}Na_1$ $[M+Na]^+$: 212.1051. Found: 212.1048.

The compound was already described in the literature:
Read, M. W.; Miller, M. L.; Ray, P. S. *Tetrahedron*, **1999**, *55*, 373.

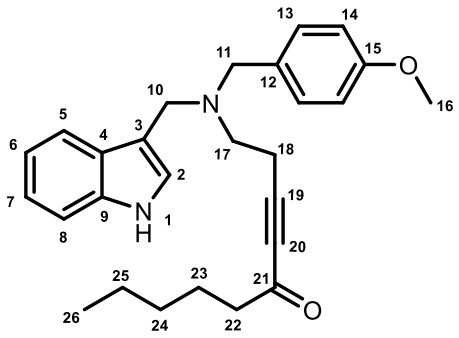
1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)dec-3-yn-5-one



To a solution of N-((1H-indol-3-yl)methyl)-N-(4-methoxybenzyl)but-3-yn-1-amine (2.1 g, 6.6 mmol, 1 eq.) in anhydrous tetrahydrofuran (40 ml) at -78°C was added *n*-butyllithium 2.5 M in hexane (15 mmol, 2.3 eq., 6.1 ml) in 2 minutes. The acetone/dry ice bath was removed to a water/ice bath for 30 minutes. The mixture was cooled to -78°C again and N-methoxy-N-methylhexanamide (1.36 g, 8.5 mmol, 1.3 eq., 1.47 ml) was added neat. The acetone/dry ice bath was removed, and the reaction was stirred for 30 minutes. The solution was purred on diethyl ether and 5M aqueous solution of ammonium chloride, the aqueous phase was extracted once with diethyl ether. The ether phases were combined and dried over sodium sulfate then the volatiles were removed in vacuum to provide a yellow-orange oil. This oil was dissolvent in acetonitrile (10 ml for 1 g of N-((1H-indol-3-yl)methyl)-N-(4-methoxybenzyl)but-3-yn-1-amine starting material) and the acetonitrile phase was washed 6 times with hexane (5 ml for 1 g of N-((1H-indol-3-yl)methyl)-N-(4-methoxybenzyl)but-3-yn-1-amine). The acetonitrile was dried again on sodium sulfate and the volatiles were removed *in vacuo* to afford the desired product as a yellow oil; 2.33 g (85%).

CAS: /

Formula: $C_{27}H_{32}N_2O_2$



Molecular weight: 416.56 g/mol

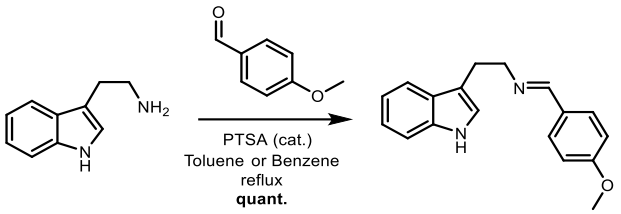
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (bs, 1H, **H1**), 7.77 – 7.72 (m, 1H, **H5**), 7.35 (dt, *J* = 8.1, 0.9 Hz, 1H, **H8**), 7.30 – 7.26 (m, 2H, **H13**), 7.22 – 7.16 (m, 1H, **H7**), 7.15 (d, *J* = 2.3 Hz, 1H, **H2**), 7.11 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, **H6**), 6.88 – 6.78 (m, 2H, **H14**), 3.81 (s, 1H, **H10**), 3.79 (s, 3H, **H16**), 3.60 (s, 2H, **H11**), 2.75 (t, *J* = 7.2 Hz, 2H, **H17**), 2.51 (t, *J* = 7.3 Hz, 2H, **H18**), 2.48 – 2.44 (m, 2H, **H22**), 1.69 – 1.56 (m, 2H, **H23**), 1.36 – 1.22 (m, 4H, **H24** + **H25**), 0.87 (t, *J* = 7.0 Hz, 3H, **H26**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 188.63 (**C21**), 158.71 (**C15**), 136.63 (**C9**), 131.56 (**C12**), 130.03 (**C13**), 127.68 (**C4**), 123.58 (**C7**), 122.10 (**C2**), 119.89 (**C5**), 119.43 (**C6**), 113.71 (**C14**), 113.41 (**C3**), 111.17 (**C8**), 93.18 (**C20**), 81.53 (**C19**), 57.73 (**C11**), 55.33 (**C16**), 51.14 (**C17**), 49.60 (**C10**), 45.51 (**C22**), 31.20 (**C24**), 23.80 (**C23**), 22.46 (**C25**), 17.73 (**C18**), 13.98 (**C26**).

IR (film, cm^{-1}): 3311 (N-H stretching), 2954 (C-H stretching), 2929 (C-H stretching), 2869 (C-H stretching), 2834 (C-H stretching), 2209 (C≡C stretching), 1662 (C=O stretching), 1611 (C=C aromatic stretching), 1584 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1456 (CH_2 scissoring), 1240 (C-N stretching), 819 (C-H bending out of plan of para disubstituted aromatic ring), 740 (C-H bending out of plan of ortho disubstituted aromatic ring).

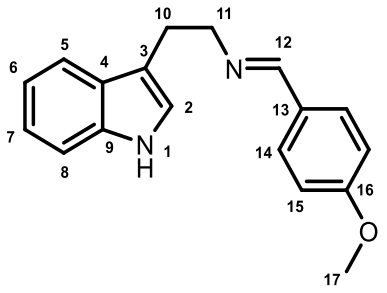
HRMS m/z calculated for $C_{27}H_{33}N_2O_2$ $[M+H]^+$: 417.2542. Found: 417.2524. **HRMS m/z calculated for $C_{27}H_{32}N_2O_2{}^{23}Na_1$ $[M+Na]^+$:** 439.2361. Found: 439.2350.

N-(2-(1H-indol-3-yl)ethyl)-1-(4-methoxyphenyl)methanimine



To a solution of tryptamine (15 g, 0.093 mol, 1 eq.) and PTSA (0.08 g, 0.4 mmol, 0.005 eq.) in toluene (180 ml) or benzene (180 ml) was added *p*-anisaldehyde (13.3 g, 0.098 mol, 1.05 eq., 11.9 ml). The resulting mixture was refluxed with a Dean-Stark apparatus until the correct amount of water (1.7 ml) was retrieved. The solvent was removed at low pressure to afford a yellow-orange solid; 26 g (quantitative).

This solid was directly used without more purification.



CAS: 93879-05-1

Formula: $C_{18}H_{18}N_2O_1$

Molecular weight: 278.35 g/mol

MP: 116-118°C **Litt**[9]**:** 119°C

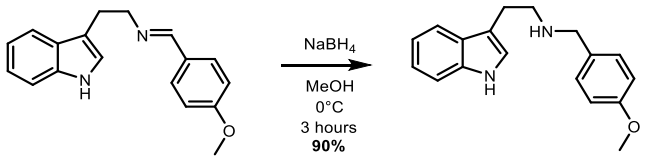
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (s, 1H, **H12**), 7.94 (bs, 1H, **H1**), 7.71 – 7.63 (m, 3H, **H5** + **H14**), 7.36 (dt, *J* = 8.0, 0.9 Hz, 1H, **H8**), 7.19 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, **H7**), 7.12 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, **H6**), 7.02 (d, *J* = 2.3 Hz, 1H, **H2**), 6.95 – 6.89 (m, 2H, **H15**), 3.90 (td, *J* = 7.4, 1.2 Hz, 2H, **H11**), 3.84 (s, 3H, **H17**), 3.15 (td, *J* = 7.3, 0.7 Hz , 2H, **H10**).

[9] Protiva *et al. Collect. Czech. Chem. Commun.*, **1963**, *28*, 629.

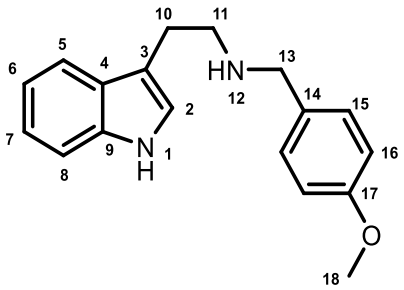
^{13}C NMR (100 MHz, $CDCl_3$) δ 161.55 (**C16**), 161.01 (**C12**), 136.31 (**C9**), 129.68 (**C14**), 129.10 (**C13**), 127.55 (**C4**), 122.33 (**C2**), 121.74 (**C7**), 119.07 (**C6**), 118.92 (**C5**), 114.01 (**C15**), 113.72 (**C3**), 111.23 (**C8**), 61.91 (**C11**), 55.28 (**C17**), 27.05 (**C10**).

IR (film, cm^{-1}): 3411 (N-H stretching), 3047 (C-H stretching), 3004 (C-H stretching), 2959 (C-H stretching), 2909 (C-H stretching), 2836 (C-H stretching), 1645 (C=N stretching), 1603 (C=C aromatic stretching), 1575 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1456 (CH_2 scissoring), 1243 (C-N stretching), 1166 (C-O stretching), 1028 (C-O stretching), 834 (C-H bending out of plan of para disubstituted aromatic ring), 737 (C-H bending out of plan of para disubstituted aromatic ring).

2-(1H-indol-3-yl)-N-(4-methoxybenzyl)ethan-1-amine



N-(2-(1H-indol-3-yl)ethyl)-1-(4-methoxyphenyl)methanimine (26 g, 0.093 mol, 1 eq.) was dissolved in methanol (200 ml) at 0°C. Then $NaBH_4$ (7.8 g, 0.206 mol, 2.2 eq.) was added portionwise and the temperature was kept below 10°C. The mixture was stirred at 0°C for 3 hours then 25-35% aqueous ammonia solution was added (150 ml) and the biphasic mixture was stirred for 2 hours. The solvent was slowly eliminated under vacuum. The resulting aqueous phase was extracted 3 time with dichloromethane, the organic layers were combined and dried over Na_2SO_4. The solvent was eliminated under low pressure providing a yellow solid which can be precipitated with diethyl ether and pentane to a white solid; 23.6 g (90%).



CAS: 7390-67-2

Formula: $C_{18}H_{20}N_2O_1$

Molecular weight: 280.37 g/mol

MP: 74-75°C **Litt:** /

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H, **H1**), 7.60 (d, *J* = 7.8 Hz, 1H, **H5**), 7.34 – 7.28 (m, 1H, **H8**), 7.21 – 7.14 (m, 3H, **H7** + **H15**), 7.13 – 7.05 (m, 1H, **H6**), 6.96 (d, *J* = 2.1 Hz, 1H, **H2**), 6.85 – 6.78 (m, 2H, **H16**), 3.77 (s, 3H, **H18**), 3.74 (s, 2H, **H13**), 3.05 – 2.90 (m, 4H, **H10** + **H11**), 1.71 (s, 1H, **H12**).

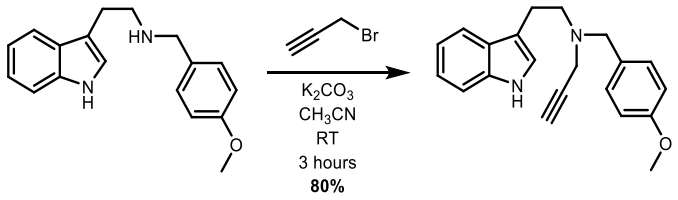
^{13}C NMR (100 MHz, $CDCl_3$) δ 158.38 (**C17**), 136.32 (**C9**), 131.81 (**C14**), 129.21 (**C15**), 127.22 (**C4**), 122.22 (**C2**), 121.51 (**C7**), 118.79 (**C6**), 118.55

(**C5**), 113.60 (**C16**), 112.85 (**C3**), 111.20 (**C8**), 54.89 (**C18**), 52.83 (**C13**), 48.98 (**C11**), 25.37 (**C10**).

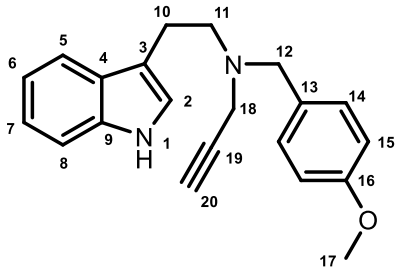
IR (film, cm^{-1}): 3412 (N-H stretching), 3054 (C-H stretching), 2915 (C-H stretching), 2834 (C-H stretching), 1610 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1454 (CH_2 scissoring), 1440 (CH_3 asymmetric deformation), 1243 (C-N stretching), 1175 (C-O stretching), 1031 (C-O stretching), 811 (C-H bending out of plan of para disubstituted aromatic ring), 737 (C-H bending out of plan of ortho disubstituted aromatic ring).

The compound was already described in the literature:
Protiva *et al. Collect. Czech. Chem. Commun.*, **1963**, *28*, 629.

N-(2-(1H-indol-3-yl)ethyl)-N-(4-methoxybenzyl)prop-2-yn-1-amine



2-(1H-indol-3-yl)-N-(4-methoxybenzyl)ethan-1-amine (6.00 g, 21.4 mmol, 1 eq.) and potassium carbonate (8.87 g, 64.2 mmol, 3 eq.) were suspended in stirring acetonitrile (120 ml) at room temperature. Then propargyl bromide (80% in toluene) (22.4 mmol, 1.05 eq., 2.42 ml) was drop wisely added and the resulting mixture was stirred for 3 hours at room temperature. Water was added, and the solution was extracted three time with dichloromethane, the organic phases were combined, and the volatiles were removed *in vacuo* to afford a yellow oil. This oil was suspended in diethyl ether, a precipitate was formed and filtered. The solvent was removed under vacuum to afford the desired product as a yellow solid; 5.45 g (80%).



CAS: /

Formula: $C_{21}H_{22}N_2O_1$

Molecular weight: 318.42 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H, **H1**), 7.58 (d, *J* = 7.8 Hz, 1H, **H5**), 7.32 – 7.24 (m, 2H, **H14**), 7.19 – 7.12 (m, 2H, **H7** + **H8**), 7.12 – 7.06 (m, 1H, **H6**), 6.89 – 6.74 (m, 3H, **H2** + **H15**), 3.70 (s, 3H, **H17**), 3.66 (s, 2H, **H12**), 3.41 (d, *J* = 2.3 Hz, 2H, **H18**), 3.03 – 2.86 (m, 4H, **H10** + **H11**), 2.26 (t, *J* = 2.3 Hz, 1H, **H20**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.70 (**C16**), 136.15 (**C9**), 130.51 (**C13**), 130.39 (**C14**), 127.47 (**C4**), 121.76 (**C2**), 121.73 (**C7**), 119.03 (**C6**), 118.80

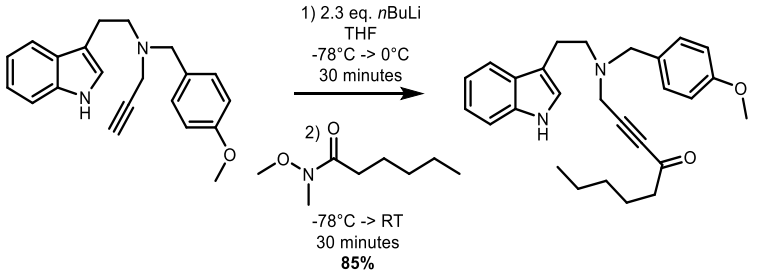
(**C5**), 113.86 (**C3**), 113.70 (**C15**), 111.16 (**C8**), 78.68 (**C19**), 73.51 (**C20**), 57.20 (**C12**), 55.12 (**C17**), 53.82 (**C11**), 41.17 (**C18**), 23.51 (**C10**).

IR (film, cm^{-1}): 3416 (N-H stretching), 3285 (C-H stretching from triple bond), 2930 (C-H stretching), 2833 (C-H stretching), 1610 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1455 (CH_2 scissoring), 1244 (C-N stretching), 1031 (C-O stretching), 815 (C-H bending out of plan of para disubstituted aromatic ring), 740 (C-H bending out of plan of ortho disubstituted aromatic ring), 637 (C-H bending out of plan of terminus alkynes).

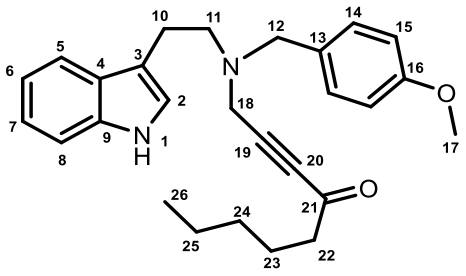
HRMS m/z calculated for $C_{21}H_{23}N_2O_1$ $[M+H]^+$: 319.1810. Found: 319.1803
HRMS m/z calculated for $C_{21}H_{22}N_2O_1{}^{23}Na_1$ $[M+Na]^+$: 341.1629. Found: 341.1615.

The compound was already described in the literature:
Magné, V.; Marinetti, A.; Gandon, V.; Voituriez, A.; Guinchard, X. *Adv. Synth. Catal*, **2017**, *359*, 4036.

1-((2-(1H-indol-3-yl)ethyl)(4-methoxybenzyl)amino)non-2-yn-4-one



To a solution of N-(2-(1H-indol-3-yl)ethyl)-N-(4-methoxybenzyl)prop-2-yn-1-amine (5.8 g, 18.2 mmol, 1 eq.) in anhydrous tetrahydrofuran (115 ml) at -78°C was added *n*-butyllithium 2.5M in hexane (41.8 mmol, 2.3 eq.) in 2 minutes. The acetone/dry ice bath was removed to a water/ice bath for 30 minutes. The mixture was cooled to -78°C again and N-methoxy-N-methylhexanamide (3.77 g, 23.7 mmol, 1.3 eq., 4.07 ml) was added neat. The acetone/dry ice bath was removed, and the reaction was stirred for 30 minutes. The solution was purred on diethyl ether and 5M aqueous solution of ammonium chloride, the aqueous phase was extracted once with diethyl ether. The ether phases were combined and dried over sodium sulfate then the volatiles were removed in vacuum to provide a yellow-orange oil. This oil was dissolvent in acetonitrile (10 ml for 1 g of N-(2-(1H-indol-3-yl)ethyl)-N-(4-methoxybenzyl)prop-2-yn-1-amine starting material) and the acetonitrile phase was washed 6 times with hexane (5 ml for 1 g of N-(2-(1H-indol-3-yl)ethyl)-N-(4-methoxybenzyl)prop-2-yn-1-amine). The acetonitrile was dried again on sodium sulfate and the volatiles were removed *in vacuo* to afford the desired product as a yellow oil; 6.5 g (85%).



CAS: /

Formula: $C_{27}H_{32}N_2O_2$

Molecular weight: 416.56 g/mol

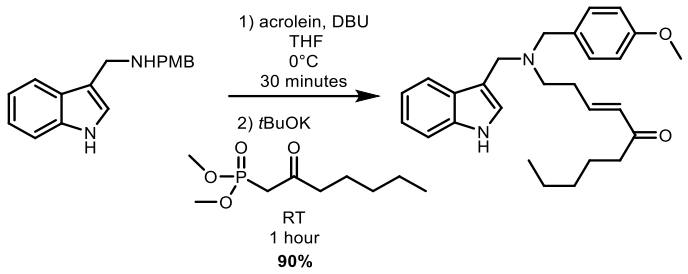
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H, **H1**), 7.57 (dd, *J* = 7.5, 0.5 Hz, 1H, **H5**), 7.35 (dt, *J* = 8.1, 0.8 Hz, 1H, **H8**), 7.30 – 7.22 (m, 2H, **H14**), 7.18 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H, **H7**), 7.10 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H, **H6**), 7.04 (d, *J* = 2.3 Hz, 1H, **H2**), 6.89 – 6.82 (m, 2H, **H15**), 3.80 (s, 3H, **H17**), 3.67 (s, 2H, **H12**), 3.57 (s, 2H, **H18**), 3.02 – 2.96 (m, 2H, **H10**), 2.96 – 2.89 (m, 2H, **H11**), 2.56 (t, *J* = 7.5 Hz, 2H, **H22**), 1.76 – 1.64 (m, 2H, **H23**), 1.38 – 1.26 (m, 4H, **H24** + **H25**), 0.89 (t, *J* = 7.0 Hz, 3H, **H26**).

^{13}C NMR (101 MHz, $CDCl_3$) δ 188.20 (**C21**), 158.91 (**C16**), 136.30 (**C9**), 130.28 (**C14**), 130.18 (**C13**), 127.47 (**C4**), 121.82 (**C2**), 121.80 (**C7**), 119.08 (**C6**), 118.70 (**C5**), 113.79 (**C15**), 113.70 (**C3**), 111.24 (**C8**), 88.46 (**C20**), 85.20 (**C19**), 57.52 (**C12**), 55.23 (**C17**), 54.13 (**C18**), 45.67 (**C22**), 41.57 (**C18**), 31.12 (**C24**), 23.88 (**C23**), 23.69 (**C10**), 22.40 (**C25**), 13.91 (**C26**).

IR (film, cm^{-1}): 3414 (N-H stretching), 2954 (C-H stretching), 2929 (C-H stretching), 2205 (C≡C stretching), 1667 (C=O stretching), 1611 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1456 (CH_2 scissoring), 1245 (C-N stretching), 1032 (C-O stretching), 817 (C-H bending out of plan of para disubstituted aromatic ring), 737 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{33}N_2O_2$ $[M+H]^+$: 417.2542. Found: 417.2534. **HRMS m/z calculated for $C_{27}H_{32}N_2O_2{}^{23}Na_1$ $[M+Na]^+$:** 439.2361. Found: 439.2356.

(*E*)-1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)dec-3-en-5-one



Solution **A**: to a solution of N-((1H-indol-3-yl)methyl)-1-(4-methoxyphenyl)methanamine (4 g, 15 mmol, 1 eq.) and 1,8-Diazabicyclo (5.4.0) undec-7-ene (0.1 g, 0.75 mmol, 0.05 eq., 0.11 ml) in tetrahydrofuran (40 ml) at 0°C was added acrolein (0.84 g, 15 mmol, 1 eq., 1.05 ml) dropwise on 1 minute, then the mixture was stirred at 0°C for 30 minutes.

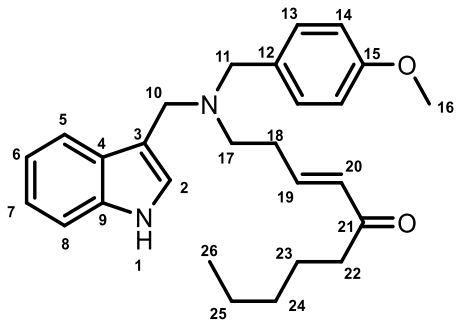
Solution **B**: to a solution of dimethyl (2-oxoheptyl)phosphonate (3.3 g, 15 mmol, 1 eq., 3.17 ml) in tetrahydrofuran (160 ml) was added solid potassium *tert*-butoxide (1.7 g, 15 mmol, 1 eq.) at room temperature, then the mixture was stirred for 20 minutes[10] at room temperature.

Solution **A** was added to Solution **B** at room temperature then the resulting mixture was stirred for 1 hour at room temperature. A saturated aqueous solution of sodium chloride was added, and the mixture was extracted two times with diethyl ether. The ether phases were combined and dried over sodium sulfate, then the volatiles were removed *in vacuo* to afford the desired product as a pale-yellow oil; 5.65 g (90%).

CAS: /

Formula: $C_{27}H_{34}N_2O_2$

[10] Tip: more time than 20-30 minutes will turn the mixture in a dense solid suspension. And will decrease the yield.



Molecular weight: 418.58 g/mol

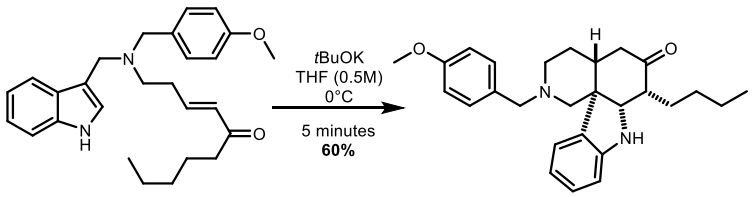
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H, **H1**), 7.69 (d, *J* = 7.9 Hz, 1H, **H5**), 7.35 – 7.31 (m, 1H, **H8**), 7.26 – 7.21 (m, 2H, **H13**), 7.20 – 7.15 (m, 1H, **H7**), 7.12 – 7.06 (m, 2H, **H2** + **H6**), 6.87 – 6.79 (m, 2H, **H14**), 6.70 (dt, *J* = 16.0, 6.9 Hz, 1H, **H19**), 6.01 (dt, *J* = 16.0, 1.4 Hz, 1H, **H20**), 3.78 (s, 3H, **H16**), 3.75 (s, 2H, **H10**), 3.54 (s, 2H, **H11**), 2.60 (t, *J* = 6.9 Hz, 2H, **H17**), 2.45 – 2.36 (m, 4H, **H18** + **H22**), 1.57 (dt, *J* = 14.8, 7.5 Hz, 2H, **H23**), 1.36 – 1.23 (m, 4H, **H24** + **H25**), 0.89 (t, *J* = 7.0 Hz, 3H, **H26**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.15 (**C21**), 158.44 (**C15**), 146.40 (**C19**), 136.55 (**C9**), 131.68 (**C12**), 130.96 (**C20**), 129.96 (**C13**), 127.58 (**C4**), 123.64 (**C2**), 121.67 (**C7**), 119.64 (**C5**), 119.01 (**C6**), 113.46 (**C14**), 112.99 (**C3**), 111.14 (**C8**), 57.61 (**C11**), 55.03 (**C16**), 51.46 (**C17**), 49.48 (**C10**), 39.39 (**C22**), 31.39 (**C24**), 30.24 (**C18**), 23.88 (**C23**), 22.42 (**C25**), 13.90 (**C26**).

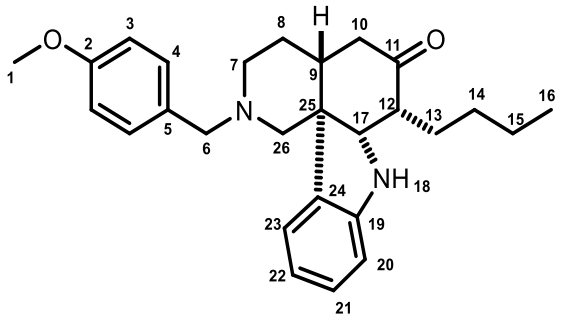
IR (film, cm^{-1}): 3356 (N-H stretching), 2953 (C-H stretching), 2929 (C-H stretching), 1662 (C=O stretching from an acyclic α, β unsaturated ketone+ C=C stretching of unsaturation), 1611 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1455 (CH_2 scissoring), 1244 (C-N stretching), 1032 (C-O stretching), 816 (C-H bending out of plan of para disubstituted aromatic ring), 738 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{35}N_2O_2$ $[M+H]^+$: 419.2698. Found: 419.2692
HRMS m/z calculated for $C_{27}H_{34}N_2O_2{}^{23}Na_1$ $[M+Na]^+$: 441.2517. Found: 441.2513.

(4aR,7R,7aS,12bS)-7-butyl-2-(4-methoxybenzyl)-1,2,3,4,4a,5,7a,8-octahydropyrido[4,3-d]carbazol-6(7H)-one



To a solution of (*E*)-1-(((1H-indol-3-yl)methyl)(4-methoxy-benzyl) amino)dec-3-en-5-one (6.3 g, 15 mmol, 1 eq.) in tetrahydrofuran (34 ml) was added solid potassium *tert*-butoxide (0.34 g, 3 mmol, 0.2 eq.) and the solution was stirred at 0°C for 5 minutes. The mixture was purred on a 5M aqueous solution of ammonium chloride and diethyl ether and vigorously shaken then extracted two times with diethyl ether. The ether phases were combined and dried over sodium sulfate. The volatiles were removed *in vacuo* to afford a yellow-brown solid. This solid was purified[11] by column chromatography using flash silica gel, petroleum ether and ethyl acetate to afford a white powder; 3.75 g (60%).



CAS: /

Formula: $C_{27}H_{34}N_2O_2$

Molecular weight: 418.58 g/mol

MP: 137-138°C **Litt**[12]**:** 89°C

[11] The product can be recrystallised from hot methanol, or from isopropanol evaporation, from recrystallisation using ethyl acetate and methanol and finally, from recrystallisation using ethyl acetate and hexane.

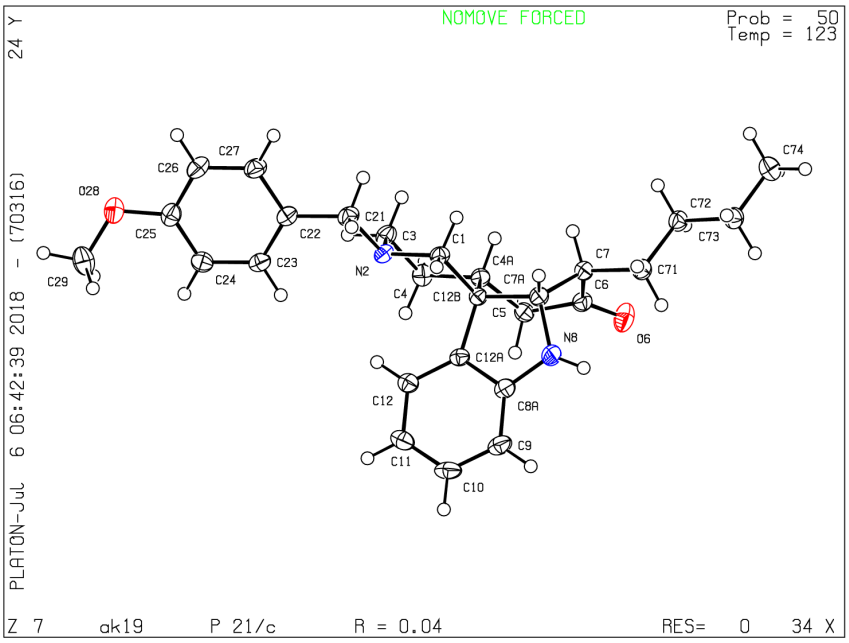
[12] Turet, L. *PhD Thesis* **2004**, Université catholique de Louvain.

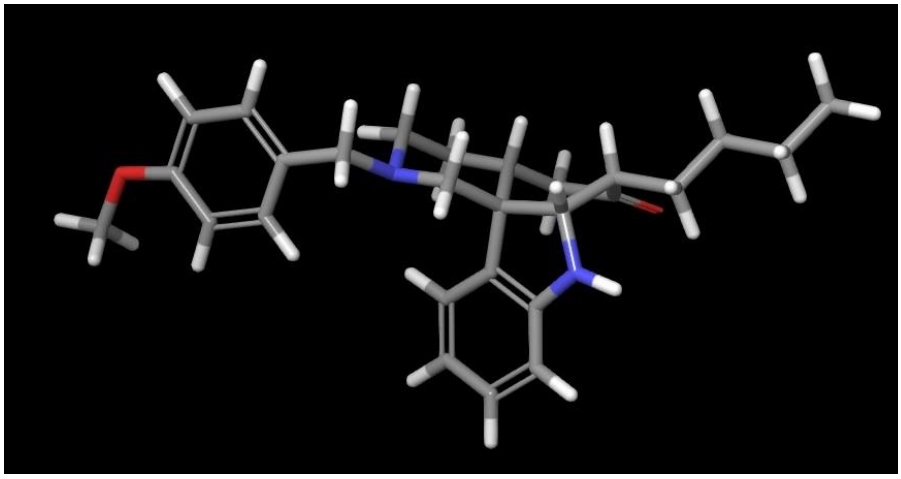
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, *J* = 7.0 Hz, 1H, **H23**), 7.19 (d, *J* = 8.6 Hz, 2H, **H4**), 7.03 (td, *J* = 7.7, 1.2 Hz, 1H, **H21**), 6.85 – 6.78 (m, 2H, **H3**), 6.70 (td, *J* = 7.5, 1.0 Hz, 1H, **H22**), 6.47 (d, *J* = 7.8 Hz, 1H, **H20**), 3.81 (bs, 1H, **H18**), 3.80 (d, *J* = 3.2 Hz, 1H, **H17**), 3.78 (s, 3H, **H1**), 3.50 (d, *J* = 13.1 Hz, 1H, **H6**), 3.41 (d, *J* = 13.1 Hz, 1H, **H6'**), 3.10 (dt, *J* = 11.0, 1.6 Hz, 1H, **H7**), 3.05 (d, *J* = 10.4 Hz, 1H, **H26**), 2.70 – 2.63 (m, 1H, **H12**), 2.29 – 2.07 (m, 4H, **H7'** + **H9** + **H10** + **H26'**), 2.07 – 1.95 (m, 1H, **H8'**), 1.95 – 1.81 (m, 2H, **H10'** + **H13**), 1.54 – 1.46 (m, 1H, **H8**), 1.44 – 1.23 (m, 5H, **H13'** + **H14** + **H15**), 0.93 (t, *J* = 7.0 Hz, 3H, **H16**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.00 (**C11**), 158.55 (**C2**), 150.44 (**C19**), 130.73 (**C5**), 130.36 (**C24**), 129.90 (**C4**), 129.25 (**C23**), 128.25 (**C21**), 117.55 (**C22**), 113.55 (**C3**), 108.49 (**C20**), 65.38 (**C26**), 64.68 (**C17**), 62.32 (**C6**), 55.17 (**C1**), 53.28 (**C7**), 49.94 (**C12**), 49.29 (**C25**), 42.45 (**C10**), 38.73 (**C9**), 29.53 (**C14**), 26.57 (**C8**), 25.08 (**C13**), 22.95 (**C15**), 14.08 (**C16**).

IR (cm^{-1}): 3381 (N-H stretching), 2931 (C-H stretching), 2868 (C-H stretching), 1712 (C=O stretching from a 6 membered ring saturated ketone), 1606 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1483 (C=C aromatic stretching), 1463 (CH_2 scissoring), 1244 (C-N stretching), 1172 (C-O stretching), 1030 (C-O stretching), 829 (C-H bending out of plan of para disubstituted aromatic ring), 734 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{35}N_2O_2$ $[M+H]^+$: 419.2698. Found: 419.2691
HRMS m/z calculated for $C_{27}H_{34}N_2O_2{}^{23}Na_1$ $[M+Na]^+$: 441.2517. Found: 441.2498.

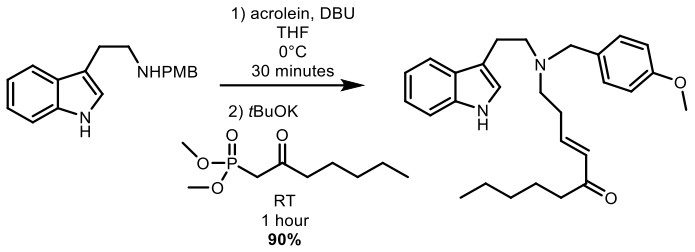

NOMOVE FORCED
Prob = 50
Temp = 123
24 Y
PLATON-Jul 6 06:42:39 2018 - (70316)
Z 7 ak19 P 21/c R = 0.04 RES= 0 34 X
C27
C26
O28
C25
C22
C21
C3
C1
C4A
C7
C74
C72
C73
C71
C23
C24
C29
N2
C4
C12B
C7A
C6
C5
O6
N8
C12A
C12
C8A
C9
C11
C10



```
Final report; processing .tmp file:
  94 unique conformations found so far
  94 minimized with good convergence
Found   17 confs within  1.00 kcal/mol ( 4.18 kJ/mol) of glob. min.
Found   44 confs within  2.00 kcal/mol ( 8.37 kJ/mol) of glob. min.
Found   60 confs within  3.00 kcal/mol (12.55 kJ/mol) of glob. min.
Found   94 confs within  5.00 kcal/mol (20.92 kJ/mol) of glob. min.
Global minimum E =   358.65 found    9 times.
 1000 steps performed so far, out of  1000
 E of low-energy structures above global min [kJ/mol],  and no. times
found:
   E:  0.00  0.43  0.59  1.11  1.21  1.80  2.61  2.86  2.90  3.25  3.30  3.45
 No.:    9   11   13   21   18    7   12   10   10   13   11   11

Input structure with title on the next line is given SerNo:       1
O=C1[C@@H](CCCC)[C@@H]([C@@]23C(CN(CC4=CC=C(OC)C=C4)C3)=C
1)NC5=C2C=CC=C5
Auto summary for input structure     1:
 Total number of structures processed =       1000
 Conformations with poor convergence marked with a *
 Conformation      1 ( 358.6519    kJ/mol) was found    9 times
 Conformation      2 ( 359.0804    kJ/mol) was found   11 times
 Conformation      3 ( 359.2433    kJ/mol) was found   13 times
 Conformation      4 ( 359.7627    kJ/mol) was found   21 times
 Conformation      5 ( 359.8592    kJ/mol) was found   18 times
 Conformation      6 ( 360.4518    kJ/mol) was found    7 times
 Conformation      7 ( 361.2623    kJ/mol) was found   12 times
 Conformation      8 ( 361.5161    kJ/mol) was found   10 times
 Conformation      9 ( 361.5558    kJ/mol) was found   10 times
 Conformation     10 ( 361.8976    kJ/mol) was found   13 times
 Conformation     11 ( 361.9515    kJ/mol) was found   11 times
 Conformation     12 ( 362.0987    kJ/mol) was found   11 times
 Conformation     13 ( 362.1584    kJ/mol) was found   16 times
 Conformation     14 ( 362.3195    kJ/mol) was found    9 times
 Conformation     15 ( 362.4659    kJ/mol) was found    9 times
```

(*E*)-1-((2-(1H-indol-3-yl)ethyl)(4-methoxybenzyl)amino)dec-3-en-5-one



Solution **A**: to a solution of 2-(1H-indol-3-yl)-N-(4-methoxybenzyl)ethan-1-amine (4 g, 14.3 mmol, 1 eq.) and 1,8-Diazabicyclo (5.4.0) undec-7-ene (0.1 g, 0.75 mmol, 0.05 eq., 0.11 ml) in tetrahydrofuran (40 ml) at 0°C was added acrolein (0.8 g, 14.3 mmol, 1 eq., 1 ml) dropwise on 1 minute, then the mixture was stirred at 0°C for 30 minutes.

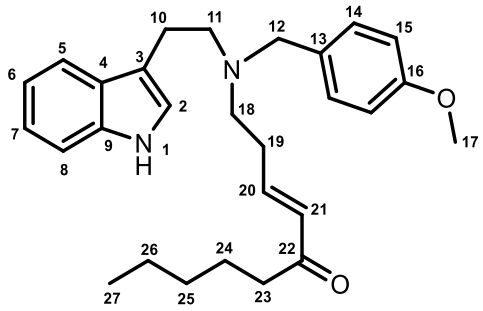
Solution **B**: to a solution of dimethyl (2-oxoheptyl)phosphonate (3.17 g, 14.2 mmol, 1 eq., 3 ml) in tetrahydrofuran (160 ml) was added solid potassium *tert*-butoxide (1.6 g, 14.2 mmol, 1 eq.) at room temperature, then the mixture was stirred for 20 minutes[13] at room temperature.

Solution **A** was added to Solution **B** at room temperature then the resulting mixture was stirred for 1 hour at room temperature. A saturated aqueous solution of sodium chloride was added, and the mixture was extracted two times with diethyl ether. The ether phases were combined and dried over sodium sulfate, then the volatiles were removed *in vacuo* to afford the desired product as a pale-yellow oil; 5.55 g (90%).

CAS: /

Formula: $C_{28}H_{36}N_2O_2$

[13] Tip: more time than 20-30 minutes will turn the mixture in a dense solid suspension. And will decrease the yield.



Molecular weight: 432.60 g/mol

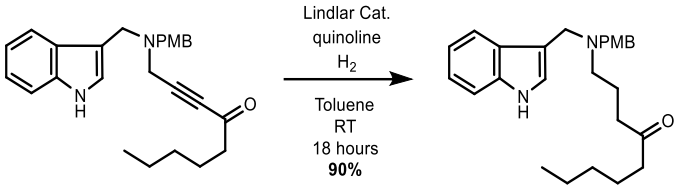
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1H, **H1**), 7.49 (d, *J* = 8.0 Hz, 1H, **H5**), 7.32 (dt, *J* = 8.1, 0.8 Hz, 1H, **H8**), 7.25 – 7.20 (m, 2H, **H14**), 7.18 – 7.13 (m, 1H, **H7**), 7.07 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H, **H6**), 6.96 (d, *J* = 2.3 Hz, 1H, **H2**), 6.86 – 6.80 (m, 2H, **H15**), 6.75 (dt, *J* = 16.0, 7.0 Hz, 1H, **H20**), 6.03 (dt, *J* = 15.9, 1.4 Hz, 1H, **H21**), 3.79 (s, 3H, **H17**), 3.63 (s, 2H, **H12**), 2.97 – 2.88 (m, 2H, **H10**), 2.84 – 2.77 (m, 2H, **H11**), 2.66 (t, *J* = 7.1 Hz, 2H, **H18**), 2.50 – 2.43 (m, 2H, **H23**), 2.36 (qd, *J* = 7.1, 1.1 Hz, 2H, **H19**), 1.65 – 1.54 (m, 2H, **H24**), 1.39 – 1.24 (m, 4H, **H25** + **H26**), 0.89 (t, *J* = 7.0 Hz, 3H, **H27**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.05 (**C22**), 158.54 (**C16**), 145.91 (**C20**), 136.27 (**C9**), 131.45 (**C13**), 131.00 (**C21**), 129.90 (**C14**), 127.44 (**C4**), 121.76 (**C2**), 121.59 (**C7**), 118.86 (**C6**), 118.58 (**C5**), 113.94 (**C3**), 113.54 (**C15**), 111.21 (**C8**), 57.75 (**C12**), 55.11 (**C17**), 54.13 (**C11**), 52.03 (**C18**), 39.73 (**C23**), 31.43 (**C25**), 30.31 (**C19**), 23.95 (**C24**), 23.03 (**C10**), 22.44 (**C26**), 13.93 (**C27**).

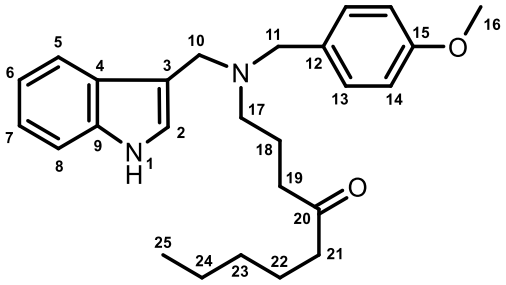
IR (film, cm^{-1}): 3408 (N-H stretching), 2952 (C-H stretching), 2929 (C-H stretching), 1663 (C=O stretching from an acyclic α, β unsaturated ketone+ C=C stretching of unsaturation), 1611 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1456 (CH_2 scissoring), 1242 (C-N stretching), 1032 (C-O stretching), 817 (C-H bending out of plan of para disubstituted aromatic ring), 737 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{28}H_{37}N_2O_2$ $[M+H]^+$: 433.2855. Found: 433.2849. **HRMS m/z calculated for $C_{28}H_{36}N_2O_2{}^{23}Na_1$ $[M+Na]^+$:** 455.2674. Found: 455.2677.

1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)nonan-4-one



Lindlar catalyst (Palladium 5% on calcium carbonate poisoned with Lead) (50 mg) was suspended in toluene (5 ml) at room temperature, quinoline (48 mg, 0.37 mmol, 0.3 eq., 0.044 ml) was added and the mixture was stirred for 30 minutes at room temperature. Then 1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)non-2-yn-4-one (0.5 g, 1.2 mmol, 1 eq.) in toluene (5 ml) was added and the mixture was flushed with hydrogen during 30 minutes at room temperature and stirred for 18 hours under hydrogen pressure. The volatiles were removed, and the brown oil was purified by column chromatography using flash silica gel, petroleum ether and diethyl ether to afford the desired product as a pale-yellow oil; 0.45 g (90%).



CAS: /

Formula: $C_{26}H_{34}N_2O_2$

Molecular weight: 406.57 g/mol

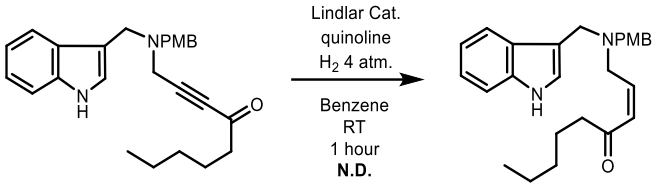
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1H, **H1**), 7.67 (dd, *J* = 7.9, 0.5 Hz, 1H, **H5**), 7.36 – 7.32 (m, 1H, **H8**), 7.24 (d, *J* = 9.0 Hz, 2H, **H13**), 7.18 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H, **H7**), 7.13 – 7.07 (m, 2H, **H2** + **H6**), 6.87 – 6.81 (m, 2H, **H14**), 3.79 (s, 3H, **H16**), 3.71 (s, 2H, **H10**), 3.51 (s, 2H, **H11**), 2.41 (t, *J* = 6.8 Hz, 2H, **H17**), 2.33 (t, *J* = 7.2 Hz, 2H, **H19**), 2.20 – 2.12 (m, 2H, **H21**), 1.76 (p, *J* = 7.0 Hz, 2H, **H18**), 1.44 (dt, *J* = 15.0, 7.4 Hz, 2H, **H22**), 1.35 – 1.13 (m, 4H, **H23** + **H24**), 0.88 (t, *J* = 7.2 Hz, 3H, **H25**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.82 (**C20**), 158.59 (**C15**), 136.58 (**C9**), 132.21 (**C12**), 130.23 (**C13**), 127.90 (**C4**), 123.58 (**C2**), 122.04 (**C7**), 119.98 (**C5**), 119.39 (**C6**), 114.01 (**C3**), 113.61 (**C14**), 111.11 (**C8**), 57.98 (**C11**), 55.35 (**C16**), 52.34 (**C17**), 49.52 (**C10**), 42.83 (**C21**), 40.35 (**C19**), 31.52 (**C23**), 23.60 (**C22**), 22.59 (**C24**), 21.30 (**C18**), 14.07 (**C25**).

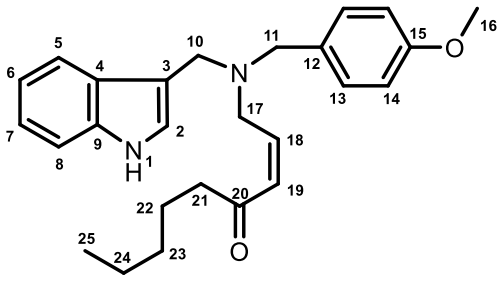
IR (film, cm^{-1}): 3411 (N-H stretching), 3056 (C-H stretching), 2997 (C-H stretching), 2952 (C-H stretching), 2929 (C-H stretching), 2869 (C-H stretching), 2833 (C-H stretching), 2802 (C-H stretching), 1702 (C=O stretching of saturated acyclic ketone), 1611 (C=C aromatic stretching), 1584 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1455 (CH_2 scissoring), 1241 (C-N stretching), 1033 (C-O stretching), 811 (C-H bending out of plan of para disubstituted aromatic ring), 738 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{26}H_{35}N_2O_2$ **$[M+H]^+$:** 407.2698. Found: 407.2693. **HRMS m/z calculated for** $C_{26}H_{34}N_2O_2{}^{23}Na_1$ **$[M+Na]^+$:** 429.2517. Found: 429.2501.

(*Z*)-1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)non-2-en-4-one



Lindlar catalyst (Palladium 5% on calcium carbonate poisoned with Lead) (0.08 g, 0.015 eq.) was suspended in benzene (15 ml) at room temperature, quinoline (160 mg, 1.24 mmol, 0.5 eq., 0.15 ml) was added and the mixture was stirred for 40 minutes at room temperature. Then 1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)non-2-yn-4-one (1 g, 2.48 mmol, 1 eq.) in benzene (10 ml) was added and the mixture was flushed with hydrogen during 30 minutes at room temperature and stirred for another 30 minutes under hydrogen pressure. The mixture was filtered through a pad of celite and eluate with diethyl ether, then the volatiles were removed to afford a pale-yellow oil. The yellow oil was used as such.[14]



CAS: /

Formula: $C_{26}H_{32}N_2O_2$

Molecular weight: 404.55 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (s, 1H, **H1**), 7.73 (d, *J* = 6.9 Hz, 1H, **H5**), 7.33 (d, *J* = 8.1 Hz, 1H, **H8**), 7.28 – 7.24 (m, 2H, **H13**), 7.21 – 7.14 (m, 1H, **H7**), 7.13 – 7.07 (m, 2H, **H2** + **H6**), 6.86 – 6.80 (m, 2H, **H14**), 6.28 (dt, *J* = 11.4, 5.6 Hz, 1H, **H18**), 6.11 (dt, *J* = 11.6, 2.2 Hz, 1H, **H19**), 3.78 (s, 3H, **H16**), 3.73 (s, 2H, **H10**), 3.63 (dd, *J* = 5.6, 2.2 Hz, 2H, **H17**), 3.53 (s, 2H, **H11**), 2.42

[14] Approximately 10% of the final weight is constituted of quinoline. And since purification by flash silica gel messed the product the following steps were made with a part of quinoline.

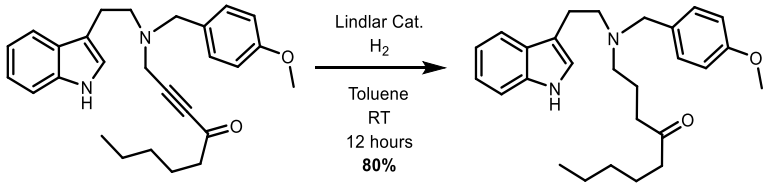
– 2.35 (m, 2H, **H21**), 1.55 (dt, *J* = 14.8, 7.4 Hz, 2H, **H22**), 1.39 – 1.20 (m, 4H, **H23** + **H24**), 0.88 (t, *J* = 7.0 Hz, 3H, **H25**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.97 (**C20**), 158.66 (**C15**), 148.98 (**C18**), 136.62 (**C9**), 131.78 (**C12**), 130.26 (**C13**), 127.83 (**C4**), 126.68 (**C19**), 123.75 (**C2**), 122.00 (**C7**), 119.97 (**C5**), 119.36 (**C6**), 113.86 (**C3**), 113.65 (**C14**), 111.13 (**C8**), 58.52 (**C11**), 55.33 (**C16**), 53.30 (**C17**), 50.29 (**C10**), 44.08 (**C21**), 31.48 (**C23**), 23.78 (**C22**), 22.58 (**C24**), 14.03 (**C25**).

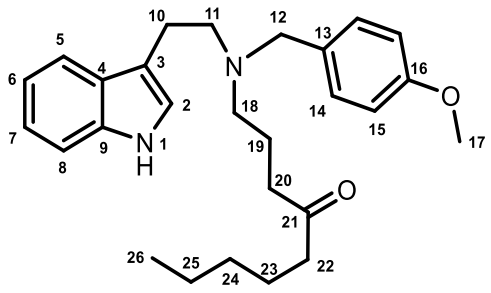
IR (film, cm^{-1}): 3342 (N-H stretching), 3057 (C-H stretching), 2954 (C-H stretching), 2929 (C-H stretching), 2870 (C-H stretching), 2834 (C-H stretching), 1671 (C=O stretching of acyclic unsaturated ketone), 1611 (C=C aromatic stretching), 1584 (C=C aromatic stretching), 1557 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1455 (CH_2 scissoring), 1244 (C-N stretching), 1100 (C-O stretching), 1034 (C-O stretching), 806 (C-H bending out of plan of para di-substituted aromatic ring), 739 (C-H bending out of plan of ortho di-substituted aromatic ring).

HRMS m/z calculated for $C_{26}H_{33}N_2O_2$ **[M+H]$^+$:** 405.2542. Found: 405.2536. **HRMS m/z calculated for** $C_{26}H_{32}N_2O_2{}^{23}Na_1$ **[M+Na]$^+$:** 427.2361. Found: 427.2355.

1-((2-(1H-indol-3-yl)ethyl)(4-methoxybenzyl)amino)nonan-4-one



Lindlar catalyst (Palladium 5% on calcium carbonate poisoned with Lead) (50 mg) was suspended in toluene (5 ml) at room temperature, then 1-((2-(1H-indol-3-yl)ethyl)(4-methoxybenzyl)amino)non-2-yn-4-one (0.5 g, 1.2 mmol, 1 eq.) in toluene (5 ml) was added and the mixture was flushed with hydrogen during 30 minutes at room temperature and stirred for 12 hours under hydrogen pressure. The volatiles were removed, and the brown oil was purified by column chromatography using flash silica gel, petroleum ether and diethyl ether to afford the desired product as a pale-yellow oil; 0.4 g (80%).



CAS: /

Formula: $C_{27}H_{36}N_2O_2$

Molecular weight: 420.59 g/mol

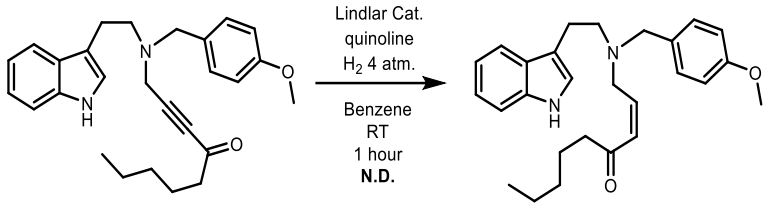
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (s, 1H, **H1**), 7.49 (d, *J* = 7.5 Hz, 1H, **H5**), 7.33 (d, *J* = 8.1 Hz, 1H, **H8**), 7.25 – 7.20 (m, 2H, **H14**), 7.20 – 7.12 (m, 1H, **H7**), 7.07 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H, **H6**), 6.96 (d, *J* = 2.3 Hz, 1H, **H2**), 6.87 – 6.81 (m, 2H, **H15**), 3.80 (s, 3H, **H17**), 3.60 (s, 2H, **H12**), 2.93 – 2.87 (m, 2H, **H10**), 2.79 – 2.73 (m, 2H, **H11**), 2.49 (t, *J* = 6.9 Hz, 2H, **H18**), 2.36 (t, *J* = 7.3 Hz, 2H, **H20**), 2.33 – 2.26 (m, 2H, **H22**), 1.74 (p, *J* = 7.1 Hz, 2H, **H19**), 1.52 (dt, *J* = 14.9, 7.5 Hz, 2H, **H23**), 1.36 – 1.17 (m, 4H, **H24** + **H25**), 0.88 (t, *J* = 7.1 Hz, 3H, **H26**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.73 (**C21**), 158.61 (**C16**), 136.32 (**C9**), 131.92 (**C13**), 130.12 (**C14**), 127.67 (**C4**), 121.89 (**C7**), 121.62 (**C2**), 119.17 (**C6**), 118.93 (**C5**), 114.68 (**C3**), 113.63 (**C15**), 111.16 (**C8**), 57.96 (**C12**), 55.33 (**C17**), 54.17 (**C11**), 52.86 (**C18**), 42.91 (**C22**), 40.41 (**C20**), 31.53 (**C24**), 23.65 (**C23**), 23.08 (**C10**), 22.57 (**C25**), 21.40 (**C19**), 14.05 (**C26**).

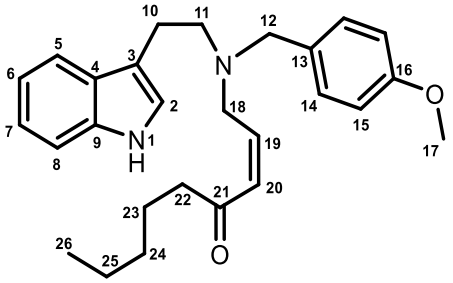
IR (film, cm^{-1}): 3410 (N-H stretching), 3056 (C-H stretching), 2996 (C-H stretching), 2952 (C-H stretching), 2929 (C-H stretching), 2857 (C-H stretching), 2807 (C-H stretching), 1703 (C=O stretching of saturated acyclic ketone), 1611 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1456 (CH_2 scissoring), 1243 (C-N stretching), 1033 (C-O stretching), 816 (C-H bending out of plan of para disubstituted aromatic ring), 738 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{37}N_2O_2$ **$[M+H]^+$:** 421.2855. **Found:** 421.2852. **HRMS m/z calculated for** $C_{27}H_{36}N_2O_2{}^{23}Na_1$ **$[M+Na]^+$:** 443.2674. **Found:** 443.2659.

(*Z*)-1-((2-(1H-indol-3-yl)ethyl)(4-methoxybenzyl)amino)non-2-en-4-one



Lindlar catalyst (Palladium 5% on calcium carbonate poisoned with Lead) (91 mg, 0.015 eq.) was suspended in benzene (20 ml) at room temperature, quinoline (186 mg, 1.44 mmol, 0.5 eq., 0.17 ml) was added and the mixture was stirred for 50 minutes at room temperature. Then 1-((2-(1H-indol-3-yl)ethyl)(4-methoxybenzyl)amino)non-2-yn-4-one (1.2 g, 2.88 mmol, 1 eq.) in benzene (12 ml) was added and the mixture was flushed with hydrogen during 30 minutes at room temperature and stirred for an additional 30 minutes under hydrogen pressure. The mixture was filtered through a pad of celite and elute with diethyl ether, then the volatiles were removed to afford a pale-yellow oil. The yellow oil was used as such. [15]



CAS: /

Formula: $C_{27}H_{34}N_2O_2$

Molecular weight: 418.58 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H, **H1)**, 7.48 (d, *J* = 7.3 Hz, 1H, **H5**), 7.32 (d, *J* = 8.1 Hz, 1H, **H8**), 7.24 (d, *J* = 8.2 Hz, 2H, **H14**), 7.21 – 7.11 (m, 1H, **H7**), 7.11 – 7.02 (m, 1H, **H6**), 6.96 (d, *J* = 2.2 Hz, 1H, **H2**), 6.86 – 6.80 (m, 2H, **H15**), 6.27 (dt, *J* = 11.6, 5.5 Hz, 1H, **H19**), 6.18 (dt, *J* = 11.6, 2.0 Hz, 1H, **H20**), 3.79 (s, 3H, **H17**), 3.74 (dd, *J* = 5.3, 2.0 Hz, 2H, **H18**), 3.63 (s, 2H, **H12**),

[15] Approximately 10% of the final weight is constituted of quinoline. And since purification by flash silica gel messed the product the following steps were made with a part of quinoline.

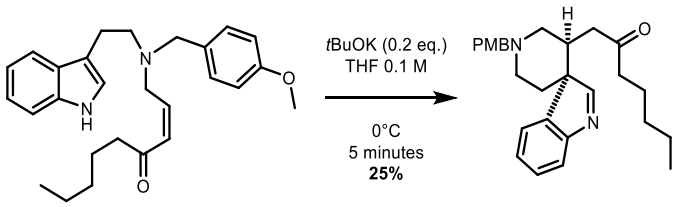
3.01 – 2.87 (m, 2H, **H10**), 2.83 – 2.74 (m, 2H, **H11**), 2.43 (t, *J* = 7.4 Hz, 2H, **H22**), 1.64 – 1.48 (m, 2H, **H23**), 1.37 – 1.18 (m, 4H, **H24** + **H25**), 0.88 (t, *J* = 7.0 Hz, 3H, **H26**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 201.94 (**C21**), 158.69 (**C16**), 148.32 (**C19**), 136.33 (**C9**), 131.36 (**C13**), 130.18 (**C14**), 127.62 (**C4**), 127.01 (**C20**), 121.80 (**C7**), 121.68 (**C2**), 119.07 (**C6**), 118.89 (**C5**), 114.38 (**C3**), 113.67 (**C15**), 111.17 (**C8**), 58.45 (**C12**), 55.29 (**C17**), 54.89 (**C11**), 53.32 (**C18**), 44.10 (**C22**), 31.45 (**C24**), 23.75 (**C23**), 23.16 (**C10**), 22.55 (**C25**), 14.00 (**C26**).

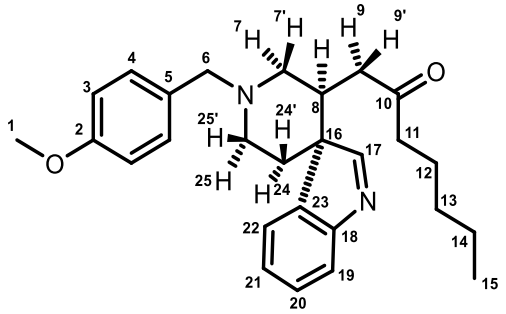
IR (film, cm^{-1}): 3306 (N-H stretching), 3056 (C-H stretching), 2953 (C-H stretching), 2929 (C-H stretching), 2857 (C-H stretching), 1670 (C=O stretching of acyclic unsaturated ketone), 1611 (C=C aromatic stretching), 1585 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1456 (CH_2 scissoring), 1245 (C-N stretching), 1101 (C-O stretching), 1033 (C-O stretching), 806 (C-H bending out of plan of para di-substituted aromatic ring), 736 (C-H bending out of plan of ortho di-substituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{35}N_2O_2$ **[M+H]$^+$:** 419.2698. Found: 419.2694. **HRMS m/z calculated for** $C_{27}H_{34}N_2O_2{}^{23}Na_1$ **[M+Na]$^+$:** 441.2517. Found: 441.2516.

1-((3S,3'S)-1'-(4-methoxybenzyl)spiro[indole-3,4'-piperidin]-3'-yl)heptan-2-one



Crude (*Z*)-1-((2-(1H-indol-3-yl)ethyl)(4-methoxybenzyl)amino)non-2-en-4-one (containing quinoline) (0.5 g, 1.2 mmol, 1 eq.) was solubilised in tetrahydrofuran (10 ml) at 0°C then solid potassium *tert*-butoxide (27 mg, 0.23 mmol, 0.2 eq.) was added and the mixture was stirred at 0°C for 5 minutes. The mixture was purred on diethyl ether and a saturated aqueous solution of ammonium chloride then extracted twice with diethyl ether, the organic phases were combined and dried over sodium sulfate. The volatiles were removed *in vacuo* to afford an orange oil. This residue was purified by column chromatography using flash silica gel, hexane and ethyl acetate to afford the desired product as pale-yellow oil; 0.12 g (25%).



CAS: /

Formula: $C_{27}H_{34}N_2O_2$

Molecular weight: 418.58 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H, **H17**), 7.63 (d, *J* = 7.6 Hz, 1H, **H19**), 7.37 – 7.31 (m, 1H, **H20**), 7.30 – 7.23 (m, 4H, **H3** + **H21** + **H22**), 6.87 (t, *J* = 8.6 Hz, 2H, **H2**), 3.80 (s, 3H, **H1**), 3.68 (d, *J* = 12.9 Hz, 1H, **H6**), 3.51 (d, *J* = 13.0 Hz, 1H, **H6'**), 3.09 (dd, *J* = 11.5, 3.4 Hz, 1H, **H7**), 2.99 (d, *J* = 11.4 Hz, 1H, **H25**), 2.93 (ddd, *J* = 12.6, 8.4, 4.4 Hz, 1H, **H8**), 2.39 – 2.30 (m, 1H, **H25'**), 2.28 (dd, *J* = 12.9, 3.2 Hz, 1H, **H24**), 2.21 (t, *J* = 11.5 Hz, 1H, **H7'**), 2.01 – 1.93 (m, 1H, **H11**), 1.90 (dd, *J* = 8.3, 6.6 Hz, 1H, **H11**), 1.83 (dd, *J* = 16.9, 8.9 Hz,

1H, **H9**), 1.46 (dd, *J* = 17.1, 3.6 Hz, 1H, **H9'**), 1.38 (d, *J* = 13.1 Hz, 1H, **H24'**), 1.34 – 1.21 (m, 2H, **H12**), 1.21 – 1.11 (m, 2H, **H14**), 1.09 – 0.98 (m, 2H, **H13**), 0.80 (t, *J* = 7.3 Hz, 3H, **H15**).

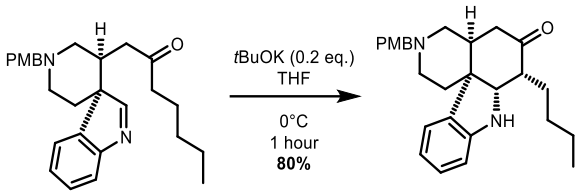
^{13}C NMR (100 MHz, $CDCl_3$) δ 209.11 (**C10**), 175.10 (**C17**), 158.83 (**C2**), 154.93 (**C18**), 141.82 (**C23**), 130.27 (**C4**), 129.86 (**C5**), 128.33 (**C20**), 126.71 (**C21**), 122.16 (**C22**), 121.15 (**C19**), 113.72 (**C3**), 62.47 (**C6**), 60.17 (**C16**), 57.73 (**C7**), 55.25 (**C1**), 51.69 (**C25**), 43.02 (**C11**), 40.86 (**C9**), 37.06 (**C8**), 33.13 (**C24**), 31.14 (**C13**), 23.22 (**C12**), 22.32 (**C14**), 13.86 (**C15**).

IR (film, cm^{-1}): 2952 (C-H stretching), 2931 (C-H stretching), 2870 (C-H stretching), 2834 (C-H stretching), 2802 (C-H stretching), 2763 (C-H stretching), 1712 (C=O stretching of acyclic saturated ketone), 1611 (C=C aromatic stretching), 1585 (C=C aromatic stretching), 1547 (C=C aromatic stretching), 1511 (C=C aromatic stretching), 1456 (CH_2 scissoring), 1344 (C-H bending in plan), 1246 (C-N stretching), 1104 (C-O stretching), 1035 (C-O stretching), 823 (C-H bending out of plan of para di-substituted aromatic ring), 754 (C-H bending out of plan of ortho di-substituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{35}N_2O_2$ **[M+H]$^+$:** 419.2698. Found: 419.2694. **HRMS m/z calculated for** $C_{27}H_{34}N_2O_2{}^{23}Na_1$ **[M+Na]$^+$:** 441.2517. Found: 441.2506.

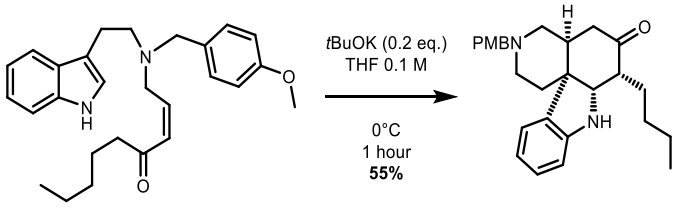
(4aS,7S,7aS,12bS)-7-butyl-3-(4-methoxybenzyl)-1,2,3,4,4a,5,7a,8-octahydropyrido[3,4-d]carbazol-6(7H)-one

Methode A:



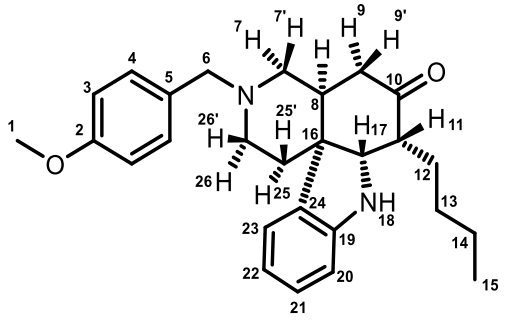
To a solution of 1-((3S,3'S)-1'-(4-methoxybenzyl)spiro[indole-3,4'-piperidin]-3'-yl)heptan-2-one (0.1 g, 0.24 mmol, 1 eq.) in tetrahydrofuran (10 ml) at 0°C was added solid potassium *tert*-butoxide (5.3 mg, 0.047 mmol, 0.2 eq.) and the mixture was stirred at 0°C for 1 hour. The mixture was purred on diethyl ether and a saturated aqueous solution of ammonium chloride then extracted twice with diethyl ether, the organic phases were combined and dried over sodium sulfate. The volatiles were removed *in vacuo* to afford an orange oil. This residue was purified by column chromatography using flash silica gel, hexane and ethyl acetate to afford the desired product as pale-yellow oil; 0.08 g (80%).

Methode B:



Crude (*Z*)-1-((2-(1H-indol-3-yl)ethyl)(4-methoxybenzyl)amino)non-2-en-4-one (containing quinoline) (0.5 g, 1.2 mmol, 1 eq.) was solubilised in tetrahydrofuran (10 ml) at 0°C then solid potassium *tert*-butoxide (27 mg, 0.23 mmol, 0.2 eq.) was added and the mixture was stirred at 0°C for 5

minutes. The mixture was purred on diethyl ether and a saturated aqueous solution of ammonium chloride then extracted twice with diethyl ether, the organic phases were combined and dried over sodium sulfate. The volatiles were removed *in vacuo* to afford an orange oil. This residue was purified by column chromatography using flash silica gel, hexane and ethyl acetate to afford the desired product as pale-yellow oil; 0.27 g (55%).



CAS: /

Formula: $C_{27}H_{34}N_2O_2$

Molecular weight: 418.58 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.0 Hz, 1H, **H23**), 7.27 (d, *J* = 8.7 Hz, 2H, **H4**), 7.07 (td, *J* = 7.6, 1.2 Hz, 1H, **H21**), 6.91 – 6.86 (m, 2H, **H4**), 6.77 (td, *J* = 7.5, 0.9 Hz, 1H, **H22**), 6.65 (d, *J* = 7.6 Hz, 1H, **H20**), 3.90 – 3.86 (m, 2H, **H17** + **H18**), 3.83 (s, 3H, **H1**), 3.60 (d, *J* = 13.0 Hz, 1H, **H6**), 3.51 (d, *J* = 13.0 Hz, 1H, **H6'**), 3.06 – 2.94 (m, 1H, **H9'**), 2.91 – 2.76 (m, 2H, **H26** + **H26'**), 2.70 (td, *J* = 6.4, 4.0 Hz, 1H, **H11**), 2.55 (dd, *J* = 12.0, 3.4 Hz, 1H, **H7**), 2.35 (dd, *J* = 12.0, 4.4 Hz, 1H, **H7'**), 2.33 – 2.24 (m, 1H, **H25'**), 2.17 (dd, *J* = 14.1, 4.9 Hz, 1H, **H9**), 2.11 (dd, *J* = 10.4, 4.5 Hz, 1H, **H8**), 2.05 – 1.97 (m, 2H, **H12** + **H25**), 1.46 – 1.25 (m, 5H, **H12** + **H13** + **H14**), 0.95 (t, *J* = 7.1 Hz, 3H, **H15**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 212.07 (**C10**), 158.66 (**C2**), 148.89 (**C19**), 137.24 (**C24**), 130.58 (**C5**), 129.87 (**C4**), 127.70 (**C21**), 124.33 (**C23**), 118.62 (**C22**), 113.60 (**C3**), 110.04 (**C20**), 72.62 (**C17**), 62.30 (**C6**), 55.18 (**C1**), 54.67 (**C7**), 50.97 (**C26**), 48.30 (**11**), 44.64 (**C16**), 42.95 (**C9**), 40.20 (**C8**), 31.56 (**C25**), 29.60 (**C13**), 25.68 (**C12**), 22.86 (**C14**), 14.01 (**C15**).

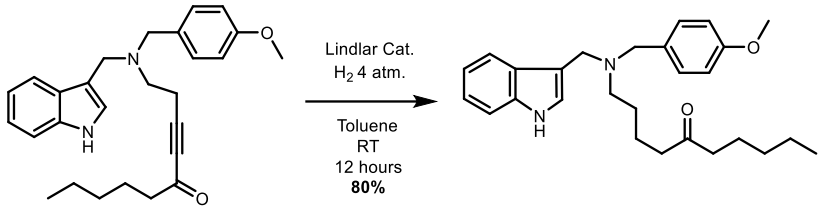
IR (film, cm^{-1}): 3358 (N-H stretching), 3035 (C-H stretching), 3002 (C-H stretching), 2953 (C-H stretching), 2931 (C-H stretching), 2870 (C-H stretching), 2814 (C-H stretching), 2769 (C-H stretching), 1711 (C=O stretching of cyclic 6-membered ring saturated ketone), 1609 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1502 (C=C aromatic

stretching), 1464 (CH_2 scissoring), 1243 (C-N stretching), 1178 (C-O stretching), 1035 (C-O stretching), 906, 805 (C-H bending out of plan of para di-substituted aromatic ring), 724 (C-H bending out of plan of ortho di-substituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{35}N_2O_2$ **$[M+H]^+$:** 419.2698. Found: 419.2693. **HRMS m/z calculated for** $C_{27}H_{34}N_2O_2{}^{23}Na_1$ **$[M+Na]^+$:** 441.2517. Found: 441.2513.

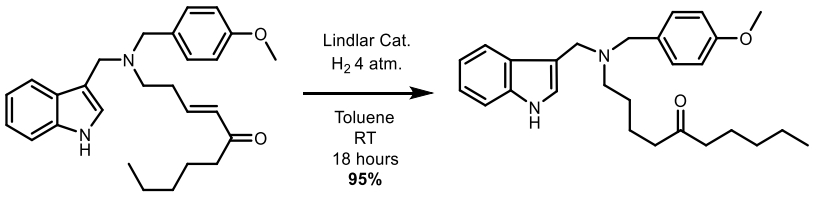
1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)decan-5-one

Methode A:



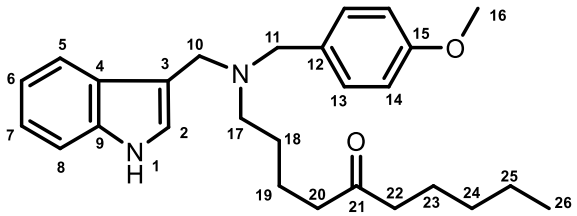
Lindlar catalyst (Palladium 5% on calcium carbonate poisoned with Lead) (50 mg) was suspended in toluene (5 ml) at room temperature, then 1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)dec-3-yn-5-one (0.5 g, 1.2 mmol, 1 eq.) in toluene (5 ml) was added and the mixture was flushed with hydrogen during 30 minutes at room temperature and stirred for 12 hours under hydrogen pressure. The mixture was filtered through a pad of celite and elute with diethyl ether, then the volatiles were removed to afford a pale-yellow oil. This oil was purified by column chromatography using flash silica gel, petroleum ether and ethyl acetate to afford the desired product as a pale-yellow oil; 0.4 g (80%).

Methode B:



Lindlar catalyst (Palladium 5% on calcium carbonate poisoned with Lead) (50 mg) was suspended in toluene (20 ml) at room temperature, then (*E*)-1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)dec-3-en-5-one (2 g, 4.7 mmol, 1 eq.) in toluene (20 ml) was added and the mixture was flushed with hydrogen during 30 minutes at room temperature and stirred for 18

hours under hydrogen pressure. The mixture was filtered through a pad of celite and elute with diethyl ether, then the volatiles were removed to afford a pale-yellow oil and this oil was purified by column chromatography using flash silica gel, petroleum ether and ethyl acetate to afford the desired product as a pale-yellow oil; 1.9 g (95%).



CAS: /

Formula: $C_{27}H_{36}N_2O_2$

Molecular weight: 420.59 g/mol

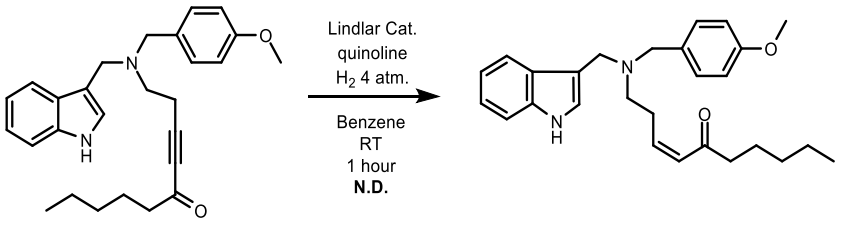
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1H, **H1**), 7.70 (d, *J* = 7.9 Hz, 1H, **H5**), 7.36 – 7.32 (m, 1H, **H8**), 7.26 – 7.22 (m, 2H, **H13**), 7.19 – 7.14 (m, 1H, **H7**), 7.12 – 7.06 (m, 2H, **H2** + **H6**), 6.86 – 6.81 (m, 2H, **H14**), 3.79 (s, 3H, **H16**), 3.72 (s, 2H, **H10**), 3.50 (s, 2H, **H11**), 2.42 (t, *J* = 6.5 Hz, 2H, **H17**), 2.28 – 2.22 (m, 2H, **H22**), 2.22 (t, *J* = 7.1 Hz, 2H, **H20**), 1.57 – 1.46 (m, 6H, **H18** + **H19** + **H23**), 1.34 – 1.17 (m, 4H, **H24** + **H25**), 0.88 (t, *J* = 7.1 Hz, 3H, **H26**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.99 (**C21**), 158.52 (**C15**), 136.54 (**C9**), 132.26 (**C12**), 130.17 (**C13**), 127.92 (**C4**), 123.51 (**C2**), 121.98 (**C7**), 119.91 (**C5**), 119.36 (**C6**), 113.97 (**C3**), 113.58 (**C14**), 111.08 (**C8**), 57.85 (**C11**), 55.33 (**C16**), 52.61 (**C17**), 49.47 (**C10**), 42.74 (**C22**), 42.38 (**C20**), 31.52 (**C24**), 26.59 (**C18**), 23.60 (**H23**), 22.56 (**C25**), 21.56 (**C19**), 14.05 (**C26**).

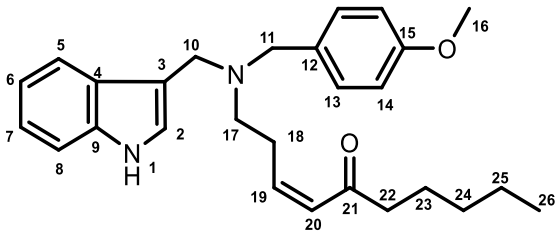
IR (film, cm^{-1}): 3412 (N-H stretching), 3057 (C-H stretching), 2997 (C-H stretching), 2951 (C-H stretching), 2930 (C-H stretching), 2860 (C-H stretching), 2833 (C-H stretching), 2797 (C-H stretching), 1703 (C=O stretching of acyclic saturated ketone), 1611 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1455 (CH_2 scissoring), 1243 (C-N stretching), 1177 (C-O stretching), 1034 (C-O stretching), 817 (C-H bending out of plan of para di-substituted aromatic ring), 741 (C-H bending out of plan of ortho di-substituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{37}N_2O_2$ **[M+H]$^+$:** 421.2855. Found: 421.2850. **HRMS m/z calculated for** $C_{27}H_{36}N_2O_2{}^{23}Na_1$ **[M+Na]$^+$:** 443.2674. Found: 443.2665.

(*Z*)-1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)dec-3-en-5-one



Lindlar catalyst (Palladium 5% on calcium carbonate poisoned with Lead) (76 mg, 0.015 eq.) was suspended in toluene (15 ml) at room temperature, quinoline (155 mg, 1.2 mmol, 0.5 eq., 0.14 ml) was added and the mixture was stirred for 50 minutes at room temperature. Then 1-(((1H-indol-3-yl)methyl)(4-methoxybenzyl)amino)dec-3-yn-5-one (1 g, 2.4 mmol, 1 eq.) in toluene (10 ml) was added and the mixture was flushed with hydrogen during 30 minutes at room temperature and stirred for an additional 30 minutes under hydrogen pressure. The mixture was filtered through a pad of celite and eluate with diethyl ether, then the volatiles were removed to afford a pale-yellow oil. The yellow oil was used as such. [16]



CAS: /

Formula: $C_{27}H_{34}N_2O_2$

Molecular weight: 418.58 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1H, **H1**), 7.70 (d, *J* = 7.1 Hz, 1H, **H5**), 7.35 – 7.32 (m, 1H, **H8**), 7.25 – 7.22 (m, 2H, **H13**), 7.20 – 7.14 (m, 1H, **H7**), 7.13 – 7.07 (m, 2H, **H2** + **H6**), 6.87 – 6.79 (m, 2H, **H14**), 6.12 (dt, *J* = 11.4, 1.5 Hz, 1H, **H20**), 6.04 (dt, *J* = 11.5, 6.7 Hz, 1H, **H19**), 3.78 (s, 3H, **H16**), 3.76 (s, 2H, **H10**), 3.54 (s, 2H, **H11**), 2.89 (qd, *J* = 6.9, 1.5 Hz, 2H, **H18**), 2.56 (t, *J*

[16] Approximately 10% of the final weight is constituted of quinoline. And since purification by flash silica gel messed the product the following steps were made with a part of quinoline.

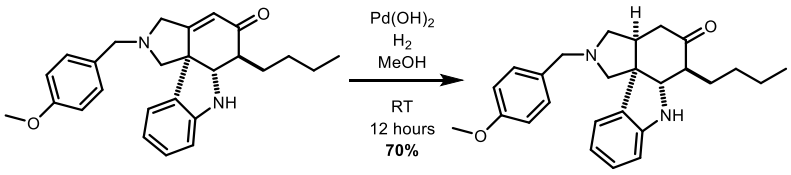
= 6.9 Hz, 2H, **H17**), 2.43 – 2.37 (m, 2H, **H22**), 1.68 – 1.48 (m, 2H, **H23**), 1.35 – 1.20 (m, 4H, **H24** + **H25**), 0.87 (t, *J* = 7.0 Hz, 3H, **H26**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 202.18 (**C21**), 158.50 (**C15**), 147.51 (**C19**), 136.60 (**C9**), 132.10 (**C12**), 130.17 (**C13**), 127.87 (**C4**), 126.87 (**C20**), 123.66 (**C2**), 121.89 (**C7**), 120.03 (**C5**), 119.24 (**C6**), 113.67 (**C3**), 113.54 (**C14**), 111.07 (**C8**), 57.40 (**C11**), 55.28 (**C16**), 52.05 (**C17**), 49.13 (**C10**), 44.31 (**C22**), 31.49 (**C24**), 27.14 (**C18**), 23.80 (**C23**), 22.56 (**C25**), 14.02 (**C26**).

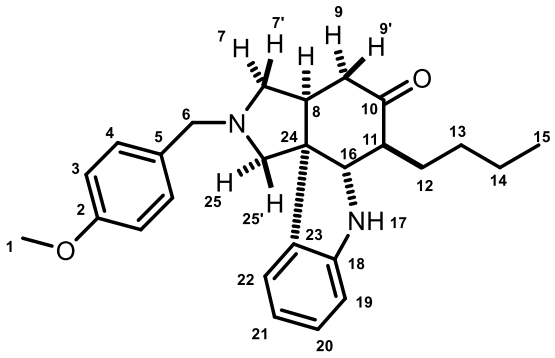
IR (film, cm^{-1}): 3351 (N-H stretching), 3057 (C-H stretching), 2953 (C-H stretching), 2929 (C-H stretching), 2859 (C-H stretching), 20833 (C-H stretching), 2807 (C-H stretching), 1685 (C=O stretching of unsaturated acyclic ketone), 1611 (C=C aromatic stretching), 1509 (C=C aromatic stretching), 1455 (CH_2 scissoring), 1240 (C-N stretching), 1171 (C-O stretching), 1033 (C-O stretching), 806 (C-H bending out of plan of para disubstituted aromatic ring), 738 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{35}N_2O_2$ **[M+H]$^+$:** 419.2698. Found: 419.2695. **HRMS m/z calculated for** $C_{27}H_{34}N_2O_2{}^{23}Na_1$ **[M+Na]$^+$:** 441.2517. Found: 441.2508.

(3aS,6S,6aS,11bS)-6-butyl-2-(4-methoxybenzyl)-2,3,3a,4,6a,7-hexahydro-1H-pyrrolo[3,4-d]carbazol-5(6H)-one



To as solution of (6S,6aS,11bS)-6-butyl-2-(4-methoxybenzyl)-2,3,6a,7-tetrahydro-1H-pyrrolo[3,4-d]carbazol-5(6H)-one (1 g, 2.48 mmol, 1 eq.) in methanol (50 ml) was added $Pd(OH)_2$ supported on carbon (0.1 g, 10% w.). The solvent and atmosphere were saturated with H_2. After 12 hours, the mixture was filtered through a pad of celite and eluted with methanol then the volatiles were removed *in vacuo*. The resulting residue was purified by column chromatography using flash silica gel, pentane and diethyl ether to afford the desired product as pale-yellow oil; 0.7 g (70%).



CAS: /

Formula: $C_{26}H_{32}N_2O_2$

Molecular weight: 404.55 g/mol

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 2H, **H4**), 7.17 (dd, *J* = 7.4, 0.6 Hz, 1H, **H22**), 7.07 (td, *J* = 7.6, 1.2 Hz, 1H, **H20**), 6.86 – 6.81 (m, 2H, **H3**), 6.79 (td, *J* = 7.5, 1.0 Hz, 1H, **H21**), 6.65 (d, *J* = 7.7 Hz, 1H, **H19**), 3.96 (s, 1H, **H17**), 3.78 (s, 3H, **H1**), 3.75 (d, *J* = 8.8 Hz, 1H, **H16**), 3.62 (d, *J* = 12.8 Hz, 1H, **H6**), 3.54 (d, *J* = 12.8 Hz, 1H, **H6'**), 3.06 (d, *J* = 9.4 Hz, 1H, **H25'**), 2.92 (dd, *J* = 9.1, 7.6 Hz, 1H, **H7**), 2.85 – 2.76 (m, 1H, **H8**), 2.55 (dd, *J* = 15.0, 5.7 Hz, 1H, **H9'**), 2.55 (d, *J* = 9.4 Hz, 2H, **H7'**+ **H25**), 2.45 (dd, *J* = 15.3, 8.9 Hz, 1H, **H9**), 2.28 (ddd, *J* = 8.8, 6.9, 4.1 Hz, 1H, **H11**), 1.72 (dddd, *J* = 14.0, 11.6, 6.8,

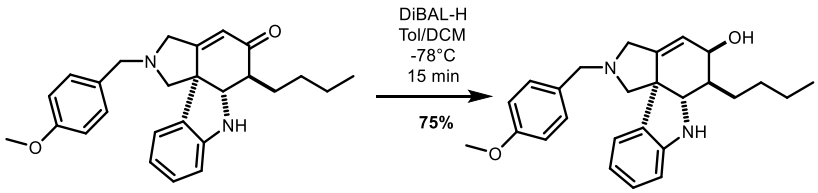
4.8 Hz, 1H, **H12**), 1.62 (ddd, *J* = 14.1, 9.9, 4.8 Hz, 1H, **H12'**), 1.37 – 1.26 (m, 3H, **H13** + **H14**), 1.25 – 1.13 (m, 1H, **H13'**), 0.90 (t, *J* = 7.1 Hz, 3H, **H15**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.84 (**C10**), 158.69 (**C2**), 148.63 (**C18**), 135.32 (**C23**), 131.06 (**C5**), 129.72 (**C4**), 128.22 (**C20**), 123.21 (**C22**), 119.40 (**C21**), 113.71 (**C3**), 109.98 (**C19**), 68.42 (**C16**), 66.27 (**C25**), 59.62 (**C7**), 59.02 (**C6**), 55.30 (**C1**), 53.99 (**C24**), 51.12 (**C11**), 43.16 (**C9**), 41.90 (**C8**), 29.23 (**C13**), 26.92 (**C12**), 23.12 (**C14**), 14.06 (**C15**).

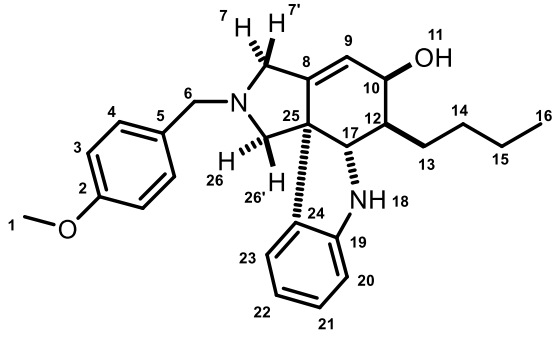
IR (film, cm^{-1}): 3367 (N-H stretching), 2954 (C-H stretching), 2929 (C-H stretching), 1705 (C=O stretching from a 6 membered ring saturated ketone), 1608 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1463 (CH_2 scissoring), 1243 (C-N stretching), 1172 (C-O stretching), 1034 (C-O stretching), 819 (C-H bending out of plan of para disubstituted aromatic ring), 725 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{26}H_{33}N_2O_2$ $[M+H]^+$: 405.2542. Found: 405.2535
HRMS m/z calculated for $C_{26}H_{32}N_2O_2{}^{23}Na_1$ $[M+Na]^+$: 427.2361. Found: 427.2350.

(5R,6S,6aS,11bS)-6-butyl-2-(4-methoxybenzyl)-2,3,5,6,6a,7-hexahydro-1H-pyrrolo[3,4-d]carbazol-5-ol



To a solution of (6S,6aS,11bS)-6-butyl-2-(4-methoxybenzyl)-2,3,6a,7-tetrahydro-1H-pyrrolo[3,4-d]carbazol-5(6H)-one (2.3 g, 5.7 mmol, 1 eq.) in dichloromethane (60 ml) at -78°C was added dropwise a 1 Molar solution of DiBAL-H in toluene (14.2 mol, 2.5 eq., 14 ml) on 2 minutes. After 15 minutes at -78°C, the reaction was quenched with a saturated aqueous solution of potassium sodium tartrate and allowed to reach room temperature and stirred for 2 additional hours. The mixture was extracted two time with dichloromethane, the organic phases were combined and dried over sodium sulfate. The volatiles were removed *in vacuo* to afford a yellow oil. The resulting residue was purified by column chromatography[17] using flash silica gel, pentane and diethyl ether to afford the desired product as an off-white solid; 1.7 g (75%).



CAS: /

Formula: $C_{26}H_{32}N_2O_2$

Molecular weight: 404.55 g/mol

MP: 47-48°C

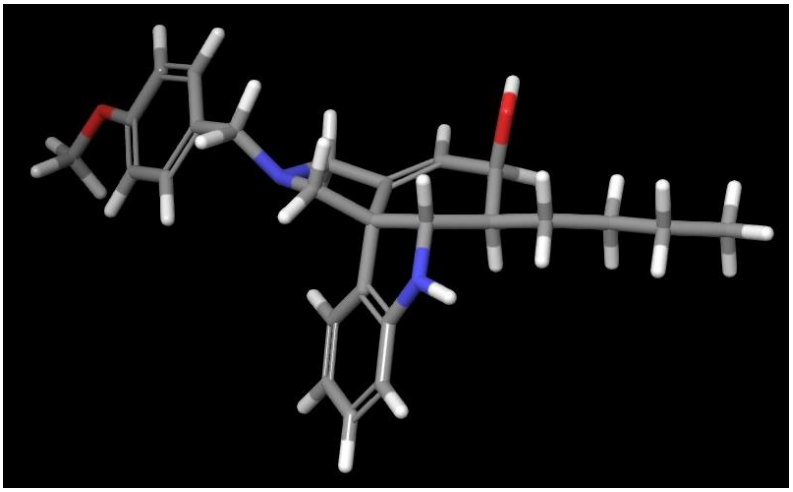
[17] Tip: the Δ RF is sufficient to separate both alcohols from each other.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.5 Hz, 1H, **H23**), 7.29 (d, *J* = 8.5 Hz, 2H, **H4**), 7.06 (td, *J* = 7.6, 1.0 Hz, 1H, **H21**), 6.86 (d, *J* = 8.6 Hz, 2H, **H3**), 6.84 – 6.76 (m, 1H, **H22**), 6.62 (d, *J* = 7.7 Hz, 1H, **H20**), 5.78 (d, *J* = 5.9 Hz, 1H, **H9**), 4.21 – 4.08 (m, 1H, **H10**), 3.92 (dd, *J* = 14.0, 1.4 Hz, 1H, **H7**), 3.86 – 3.76 (m, 2H, **H6** + **H17**), 3.80 (s, 3H, **H1**), 3.66 (d, *J* = 13.0 Hz, 1H, **H6'**), 3.11 (d, *J* = 7.6 Hz, 1H, **H26**), 3.10 (d, *J* = 15.2 Hz, 1H, **H7'**), 2.49 (d, *J* = 8.0 Hz, 1H, **H26'**), 2.08 – 2.00 (m, 1H, **H12**), 1.39 – 1.29 (m, 5H, **H13** + **H14** + **H15**), 1.29 – 1.18 (m, 1H, **H13'**), 0.91 (t, *J* = 6.9 Hz, 3H, **H16**).

^{13}C NMR (100MHz, $CDCl_3$) δ 158.58 (**C2**), 147.46 (**C19**), 143.08 (**C8**), 135.12 (**C24**), 131.31 (**C5**), 129.52 (**C4**), 127.99 (**C21**), 125.22 (**C23**), 120.43 (**C9**), 119.91 (**C22**), 113.70 (**C3**), 110.05 (**C20**), 68.60 (**C10**), 65.48 (**C26**), 63.70 (**C17**), 59.49 (**C6**), 55.44 (**C7**), 55.22 (**C1**), 53.55 (**C25**), 44.26 (**C12**), 30.25 (**C13**), 29.40 (**C14**), 22.96 (**C15**), 14.07 (**C16**).

IR (film, cm^{-1}): 3336 (O-H stretching + N-H stretching), 2953 (C-H stretching), 2927 (C-H stretching), 1607 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1462 (CH_2 scissoring), 1242 (C-N stretching), 1022 (C-O stretching), 908, 817 (C-H bending out of plan of para disubstituted aromatic ring, 730 (C-H bending out of plan of ortho disubstituted aromatic ring).

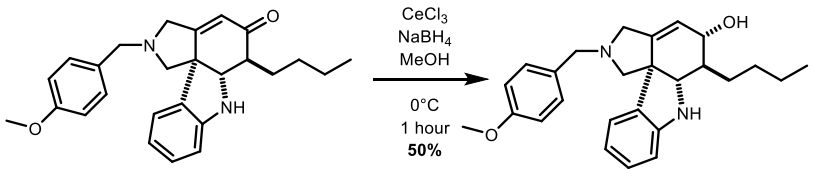
HRMS m/z calculated for $C_{26}H_{33}N_2O_2$ $[M+H]^+$: 405.2542. Found: 405.2533. **HRMS m/z calculated for $C_{26}H_{32}N_2O_2{}^{23}Na_1$ $[M+Na]^+$:** 427.2361. Found: 427.2357.



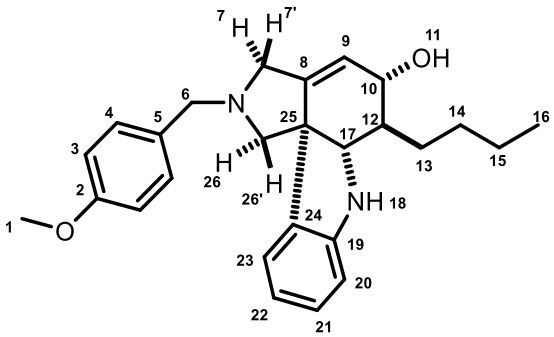
Final report; processing .tmp file:
241 unique conformations found so far
241 minimized with good convergence
Found 11 confs within 1.00 kcal/mol (4.18 kJ/mol) of glob. min.
Found 40 confs within 2.00 kcal/mol (8.37 kJ/mol) of glob. min.
Found 77 confs within 3.00 kcal/mol (12.55 kJ/mol) of glob. min.
Found 240 confs within 5.00 kcal/mol (20.92 kJ/mol) of glob. min.
Found 241 confs within 10.00 kcal/mol (41.84 kJ/mol) of glob. min.
Global minimum E = 384.05 found 8 times.
1000 steps performed so far, out of 1000
E of low-energy structures above global min [kJ/mol], and no. times found:
E: 0.00 1.70 1.88 2.90 3.13 3.31 3.61 3.63 3.87 4.08 4.14 4.48
No.: 8 4 7 7 5 6 4 5 1 2 4 6

Input structure with title on the next line is given SerNo: 1
O=C1[C@@H](CCCC)[C@@H]([C@@]23C(CN(CC4=CC=C(OC)C=C4)C3)=C1)NC5=C2C=CC=C5
Auto summary for input structure 1:
Total number of structures processed = 1000
Conformations with poor convergence marked with a *
Conformation 1 (384.0497 kJ/mol) was found 8 times
Conformation 2 (385.7525 kJ/mol) was found 4 times
Conformation 3 (385.9331 kJ/mol) was found 7 times
Conformation 4 (386.9464 kJ/mol) was found 7 times
Conformation 5 (387.1773 kJ/mol) was found 5 times
Conformation 6 (387.3549 kJ/mol) was found 6 times
Conformation 7 (387.6554 kJ/mol) was found 4 times
Conformation 8 (387.6832 kJ/mol) was found 5 times
Conformation 9 (387.9191 kJ/mol) was found 1 times
Conformation 10 (388.1345 kJ/mol) was found 2 times
Conformation 11 (388.1875 kJ/mol) was found 4 times
Conformation 12 (388.5331 kJ/mol) was found 6 times
Conformation 13 (388.5791 kJ/mol) was found 4 times
Conformation 14 (388.6996 kJ/mol) was found 3 times
Conformation 15 (388.7537 kJ/mol) was found 4 times

(5S,6S,6aS,11bS)-6-butyl-2-(4-methoxybenzyl)-2,3,5,6,6a,7-hexahydro-1H-pyrrolo[3,4-d]carbazol-5-ol



To as solution of (6S,6aS,11bS)-6-butyl-2-(4-methoxybenzyl)-2,3,6a,7-tetrahydro-1H-pyrrolo[3,4-d]carbazol-5(6H)-one (1.2 g, 2.98 mmol, 1 eq.) in methanol (60 ml) at 0°C was added cerium trichloride heptahydrate (2.2 g, 5.96 mmol, 2 eq.) and the mixture was stirred for 30 minutes. Then sodium borohydride (135 mg, 3.57 mmol, 1.2 eq.) was added portion wise on 15 minutes. The mixture was stirred for an additional 5 minutes then quenched a 25% aqueous solution of ammonia and left under stirring for 3 hours at room temperature. The mixture was extracted with dichloromethane, the organic phases were combined and dried over sodium sulfate. The volatiles were removed *in vacuo* to afford a yellow-brown oil. The resulting residue was purified by column chromatography[18] using flash silica gel, pentane and diethyl ether to afford the desired product as an off-white solid; 0.6 g (50%[19]).



CAS: /

Formula: $C_{26}H_{32}N_2O_2$

Molecular weight: 404.55 g/mol

[18] Tip: the Δ RF is sufficient to separate both alcohols from each other.

[19] Tip: 1-gram scale appears to be the worse in term of facial selectivity and decrease the yield in the target product. (1 g = 6/4 when 0.1 g = 8/2).

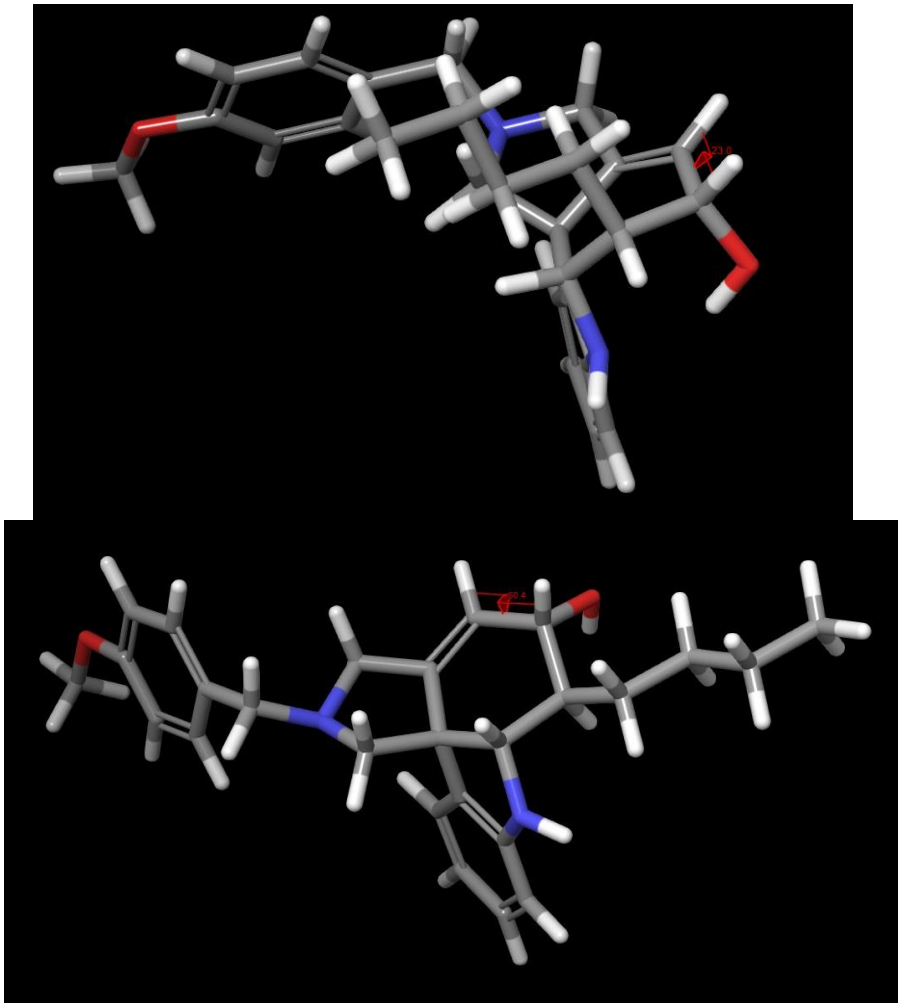
MP: 49-52°C

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 7.4, 0.8 Hz, 1H, **H23**), 7.25 (d, *J* = 8.6 Hz, 2H, **H4**), 7.04 (td, *J* = 7.6, 1.2 Hz, 1H, **H21**), 6.89 – 6.80 (m, 2H, **H3**), 6.72 (td, *J* = 7.4, 0.9 Hz, 1H, **H22**), 6.59 (d, *J* = 7.7 Hz, 1H, **H20**), 5.61 (dt, *J* = 1.8, 1.6 Hz, 1H, **H9**), 4.26 – 4.23 (m, 1H, **H10**), 3.89 (dt, *J* = 14.2, 2.1 Hz, 1H, **H7**), 3.79 (s, 3H, **H1**), 3.76 (d, *J* = 13.5 Hz, 1H, **H6**), 3.58 (d, *J* = 13.0 Hz, 1H, **H6'**), 3.56 (d, *J* = 6.9 Hz, 1H, **H17**), 3.09 (d, *J* = 12.6 Hz, 1H, **H7'**), 3.06 (d, *J* = 7.8 Hz, 1H, **H26**), 2.48 (d, *J* = 8.0 Hz, 1H, **H26'**), 1.72 – 1.64 (m, 1H, **H12**), 1.64 – 1.52 (m, 1H, **H13**), 1.47 – 1.20 (m, 5H, **H13'**+ **H14** + **H15**), 0.90 (t, *J* = 7.0 Hz, 3H, **H16**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.67 (**C2**), 149.12 (**C19**), 142.03 (**C8**), 135.08 (**C24**), 131.41 (**C5**), 129.64 (**C4**), 127.88 (**C21**), 124.88 (**C23**), 121.86 (**C9**), 118.68 (**C22**), 113.77 (**C3**), 109.35 (**C20**), 66.69 (**C26**), 66.13 (**C10**), 62.25 (**C17**), 59.35 (**C6**), 56.30 (**C7**), 55.36 (**C1**), 55.19 (**C25**), 44.37 (**C12**), 29.65 (**C14**), 26.60 (**C13**), 23.23 (**C15**), 14.19 (**C16**).

IR (film, cm^{-1}): 3387 (O-H stretching + N-H stretching), 2953 (C-H stretching), 2928 (C-H stretching), 1603 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1481 (C=C aromatic stretching), 1462 (CH_2 scissoring), 1242 (C-N stretching), 1029 (C-O stretching), 908, 820 (C-H bending out of plan of para disubstituted aromatic ring, 730 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{26}H_{33}N_2O_2$ $[M+H]^+$: 405.2542. Found: 405.2533.
HRMS m/z calculated for $C_{26}H_{32}N_2O_2{}^{23}Na_1$ $[M+Na]^+$: 427.2361. Found: 427.2354.

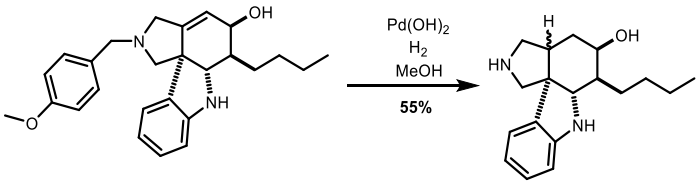


Final report; processing .tmp file:
226 unique conformations found so far
226 minimized with good convergence
Found 22 confs within 1.00 kcal/mol (4.18 kJ/mol) of glob. min.
Found 58 confs within 2.00 kcal/mol (8.37 kJ/mol) of glob. min.
Found 103 confs within 3.00 kcal/mol (12.55 kJ/mol) of glob. min.
Found 226 confs within 5.00 kcal/mol (20.92 kJ/mol) of glob. min.
Global minimum E = 383.02 found 5 times.
1000 steps performed so far, out of 1000
E of low-energy structures above global min [kJ/mol], and no. times found:

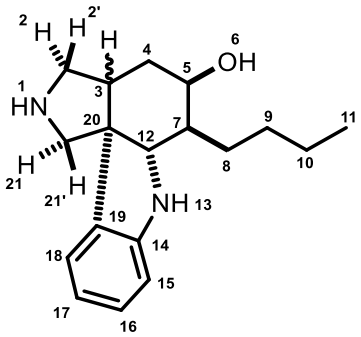
E: 0.00 0.49 0.54 0.72 1.42 1.55 1.56 1.58 1.60 1.61 2.55 2.63
No.: 5 6 5 3 4 5 6 5 10 2 10 7

Input structure with title on the next line is given SerNo: 1
O=C1[C@@H](CCCC)[C@@H]([C@@]23C(CN(CC4=CC=C(OC)C=C4)C3)=C1)NC5=C2C=CC=C5
Auto summary for input structure 1:
Total number of structures processed = 1000
Conformations with poor convergence marked with a *
Conformation 1 (383.0155 kJ/mol) was found 5 times
Conformation 2 (383.5075 kJ/mol) was found 6 times
Conformation 3 (383.5546 kJ/mol) was found 5 times
Conformation 4 (383.7386 kJ/mol) was found 3 times
Conformation 5 (384.4391 kJ/mol) was found 4 times
Conformation 6 (384.5617 kJ/mol) was found 5 times
Conformation 7 (384.5798 kJ/mol) was found 6 times
Conformation 8 (384.5994 kJ/mol) was found 5 times
Conformation 9 (384.6167 kJ/mol) was found 10 times
Conformation 10 (384.6298 kJ/mol) was found 2 times
Conformation 11 (385.5630 kJ/mol) was found 10 times
Conformation 12 (385.6447 kJ/mol) was found 7 times
Conformation 13 (385.7111 kJ/mol) was found 7 times
Conformation 14 (385.9957 kJ/mol) was found 5 times
Conformation 15 (386.1260 kJ/mol) was found 2 times

(3aS,5R,6S,6aS,11bS)-6-butyl-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[3,4-d]carbazol-5-ol



To a solution of (6S,6aS,11bS)-6-butyl-2-(4-methoxybenzyl)-2,3,6a,7-tetrahydro-1H-pyrrolo[3,4-d]carbazol-5(6H)-one (0.5 g, 1.23 mmol, 1 eq.) in methanol (15 ml) at room temperature was added $Pd(OH)_2$ supported on carbon (0.05 g, 10% w.). The solvent and atmosphere were saturated with H_2 and the mixture was stirred under hydrogen pressure for 4 days. The mixture was filtered through a pad of celite and eluted with methanol then the volatiles were removed *in vacuo*. The resulting residue was purified by column chromatography using flash silica gel, dichloromethane and methanol to afford an off-white solid; 0.19 g (55%).



CAS: /

Formula: $C_{18}H_{26}N_2O$

Molecular weight: 286.42 g/mol

MP: 54-56°C **Litt:** /

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 7.4 Hz, 1H, **H18**), 7.06 (td, *J* = 7.6, 1.2 Hz, 1H, **H16**), 6.82 (td, *J* = 7.5, 0.9 Hz, 1H, **H17**), 6.68 (d, *J* = 7.6 Hz, 1H, **H15**), 4.03 (bs, 1H, **H13**), 3.86 (dd, *J* = 7.9, 5.0 Hz, 1H, **H5**), 3.68 (d, *J* = 4.2 Hz, 1H, **H12**), 3.36 (dd, *J* = 11.0, 6.9 Hz, 1H, **H2**), 3.24 (d, *J* = 11.4 Hz, 1H, **H21**), 3.15 (d, *J* = 11.4 Hz, 1H, **H21**), 2.85 (dd, *J* = 11.0, 2.9 Hz, 1H, **H2**), 2.37

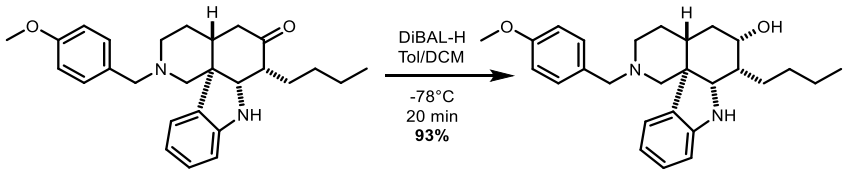
(dtd, *J* = 9.4, 6.5, 2.9 Hz, 1H, **H3**), 1.96 – 1.86 (m, 1H, **H7**), 1.79 – 1.64 (m, 2H, **H4**), 1.53 – 1.28 (m, 6H, **H8** + **H9** + **H10**), 0.91 (t, *J* = 7.0 Hz, 3H, **H11**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 148.52 (**C14**), 135.75 (**C19**), 127.32 (**C16**), 121.83 (**C18**), 119.31 (**C17**), 109.90 (**C15**), 67.67 (**C5**), 65.56 (**C12**), 56.88 (**C21**), 53.40 (**C20**), 51.04 (**C2**), 43.67 (**C7**), 38.64 (**C3**), 31.86 (**C4**), 29.83 (**C8**), 28.98 (**C9**), 22.80 (**C10**), 13.82 (**C11**).

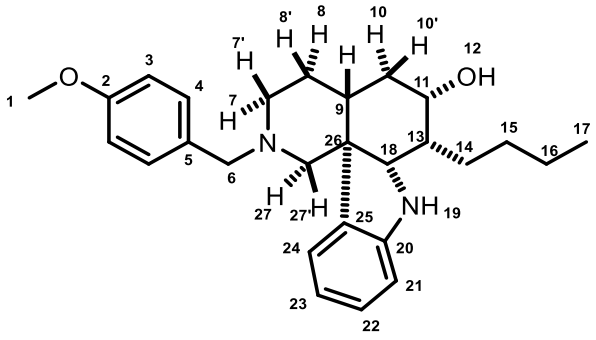
IR (cm^{-1}): 3322 (O-H Stretching + N-H stretching), 2953 (C-H stretching), 2926 (C-H stretching), 2869 (C-H stretching), 1606 (C=C aromatic stretching), 1481 (C=C aromatic stretching), 1462 (CH_2 scissoring), 1263 (C-N stretching), 907, 748 (C-H bending out of plan of ortho di-substituted aromatic ring), 728 (C-H bending out of plan of ortho di-substituted aromatic ring).

HRMS m/z calculated for $C_{18}H_{27}N_2O_1$ $[M+H]^+$: 287.2123. Found: 287.2111.

(4aR,6S,7R,7aS,12bS)-7-butyl-2-(4-methoxybenzyl)-1,2,3,4,4a,5,6,7,7a,8-decahydropyrido[4,3-d]carbazol-6-ol



To a solution of (4aR,7R,7aS,12bS)-7-butyl-2-(4-methoxybenzyl)-1,2,3,4,4a,5,7a,8-octahydropyrido[4,3-d]carbazol-6(7H)- (1 g, 2.39 mmol, 1 eq.) in dichloromethane (30 ml) at -78°C was added dropwise a solution of DiBAL-H in toluene (6 ml, 5.97 mmol, 2.5 eq.). After 20 minutes at -78°C, the reaction was quenched with a saturated aqueous potassium sodium tartrate then allowed to reach room temperature and stirred for 2 additional hours. The mixture was extracted two time with dichloromethane, the organic phases were combined and dried over sodium sulfate. The volatiles were removed *in vacuo* to afford a yellow oil. The resulting residue was purified by column chromatography using flash silica gel, pentane and diethyl ether to afford the desired product as an off-white solid; 9.3 g (93%).



CAS: /

Formula:
$C_{27}H_{36}N_2O_2$

Molecular weight:
420.59 g/mol

MP: 54-55°C **Litt:** /

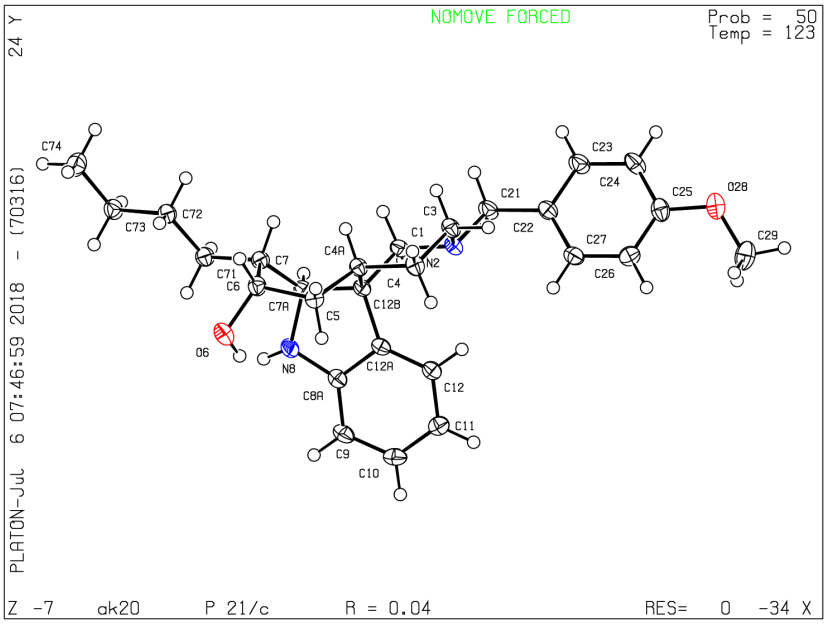
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (dd, *J* = 7.6, 0.8 Hz, 1H, **H24**), 7.23 – 7.17 (m, 2H, **H4**), 7.09 (td, *J* = 7.6, 1.3 Hz, 1H, **H22**), 6.82 – 6.80 (m, 2H, **H3**), 6.81 (td, *J* = 7.4, 1.0 Hz, 1H, **H23**), 6.61 (dd, *J* = 7.8, 0.6 Hz, 1H, **H21**), 4.06 – 3.90 (m, 2H, **H11** + **H19**), 3.78 (s, 3H, **H1**), 3.51 – 3.47 (m, 1H, **H18**), 3.45 (d, *J* =

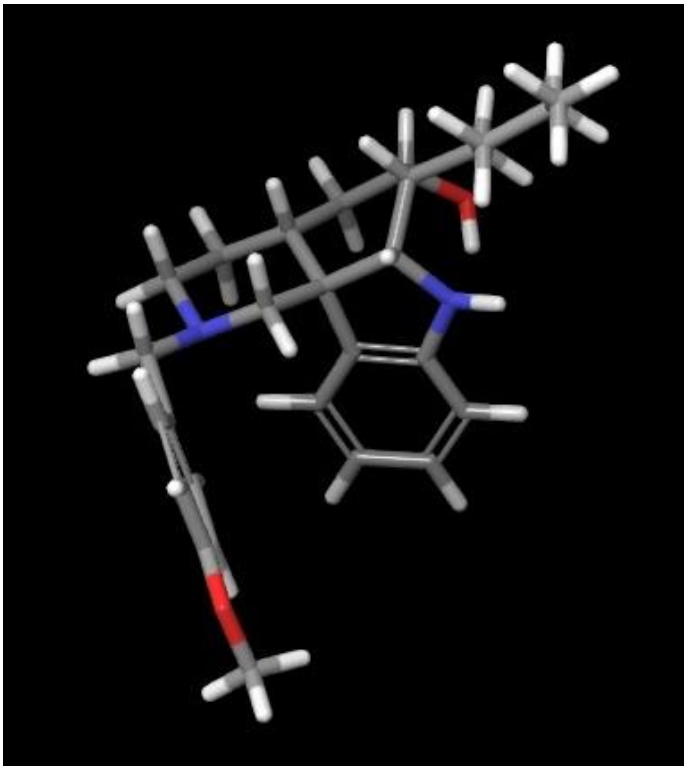
13.2 Hz, 1H, **H6**), 3.38 (d, *J* = 13.0 Hz, 1H, **H6'**), 3.20 (d, *J* = 11.0 Hz, 1H, **H12**), 3.08 (dt, *J* = 10.8, 1.7 Hz, 1H, **H7**), 2.86 (d, *J* = 10.2 Hz, 1H, **H27**), 2.11 – 2.01 (m, 2H, **H7'** + **H10'**), 1.99 (d, *J* = 10.2 Hz, 1H, **H27'**), 1.88 (dd, *J* = 12.5, 4.1 Hz, 1H, **H8**), 1.81 – 1.71 (m, 1H, **H14**), 1.71 – 1.60 (m, 1H, **H13**), 1.55 – 1.26 (m, 7H, **H8'** + **H9** + **H14'** + **H15** + **H16**), 1.04 – 0.88 (m, 4H, **H17** + **H10**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.65 (**C2**), 149.79 (**C20**), 132.86 (**C25**), 131.12 (**C5**), 130.22 (**C24**), 130.10 (**C4**), 128.09 (**C22**), 119.04 (**C23**), 113.66 (**C3**), 110.10 (**C21**), 69.27 (**C11**), 66.07 (**C18**), 65.76 (**C27**), 62.60 (**C6**), 55.35 (**C1**), 54.26 (**C7**), 49.47 (**C26**), 39.12 (**C9**), 38.74 (**C13**), 37.44 (**C10**), 29.62 (**C15**), 28.93 (**C14**), 26.79 (**C8**), 23.23 (**C16**), 14.28 (**C17**).

IR (film, cm^{-1}): 3347 (O-H stretching + N-H stretching), 2928 (C-H stretching), 2858 (C-H stretching), 1609 (C=C aromatic stretching), 1587 (C=C aromatic stretching), 1510 (C=C aromatic stretching), 1483 (C=C aromatic stretching), 1463 (CH_2 scissoring), 1243 (C-N stretching), 1033 (C-O stretching), 827 (C-H bending out of plan of para disubstituted aromatic ring, 747 (C-H bending out of plan of ortho disubstituted aromatic ring).

HRMS m/z calculated for $C_{27}H_{37}N_2O_2$ $[M+H]^+$: 421.2855. Found: 421.2853
HRMS m/z calculated for $C_{27}H_{36}N_2O_2{}^{23}Na_1$ $[M+Na]^+$: 443.2674. Found: 443.2657.

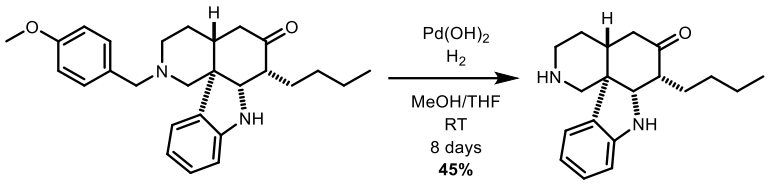

NOMOVE FORCED
Prob = 50
Temp = 123
24 Y
PLATON-Jul 6 07:46:59 2018 - (70316)
C74
C73
C72
C71
C6
C7
C7A
C5
C4
C4A
C12B
C1
C3
N2
C21
C22
C23
C24
C25
O28
C29
C27
C26
O6
N8
C12A
C8A
C12
C11
C9
C10
Z -7 ak20 P 21/c R = 0.04 RES= 0 -34 X



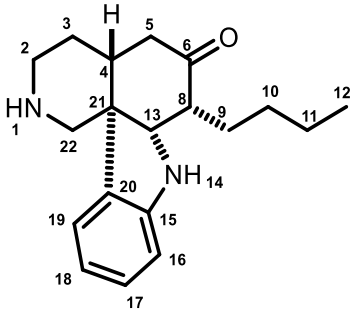
Final report; processing .tmp file:
103 unique conformations found so far
103 minimized with good convergence
Found 19 confs within 1.00 kcal/mol (4.18 kJ/mol) of glob. min.
Found 45 confs within 2.00 kcal/mol (8.37 kJ/mol) of glob. min.
Found 57 confs within 3.00 kcal/mol (12.55 kJ/mol) of glob. min.
Found 102 confs within 5.00 kcal/mol (20.92 kJ/mol) of glob. min.
Found 103 confs within 10.00 kcal/mol (41.84 kJ/mol) of glob. min.
Global minimum E = 397.51 found 7 times.
1000 steps performed so far, out of 1000
E of low-energy structures above global min [kJ/mol], and no. times found:
E: 0.00 0.14 0.31 0.46 1.46 1.61 2.12 2.23 2.25 2.61 2.89 3.02
No.: 7 9 9 17 7 11 11 11 12 11 8 11

Input structure with title on the next line is given SerNo: 1
O=C1[C@@H](CCCC)[C@@H]([C@@]23C(CN(CC4=CC=C(OC)C=C4)C3)=C1)NC5=C2C=CC=C5
Auto summary for input structure 1:
Total number of structures processed = 1000
Conformations with poor convergence marked with a *
Conformation 1 (397.5088 kJ/mol) was found 7 times
Conformation 2 (397.6481 kJ/mol) was found 9 times
Conformation 3 (397.8218 kJ/mol) was found 9 times
Conformation 4 (397.9730 kJ/mol) was found 17 times
Conformation 5 (398.9704 kJ/mol) was found 7 times
Conformation 6 (399.1152 kJ/mol) was found 11 times
Conformation 7 (399.6242 kJ/mol) was found 11 times
Conformation 8 (399.7419 kJ/mol) was found 11 times
Conformation 9 (399.7550 kJ/mol) was found 12 times
Conformation 10 (400.1194 kJ/mol) was found 11 times
Conformation 11 (400.3948 kJ/mol) was found 8 times
Conformation 12 (400.5244 kJ/mol) was found 11 times
Conformation 13 (400.6304 kJ/mol) was found 12 times
Conformation 14 (400.7063 kJ/mol) was found 8 times
Conformation 15 (400.8584 kJ/mol) was found 9 times

(4aR,7R,7aS,12bS)-7-butyl-1,2,3,4,4a,5,7a,8-octahydropyrido[4,3-d]carbazol-6(7H)-one



To a solution of (4aR,7R,7aS,12bS)-7-butyl-2-(4-methoxybenzyl)-1,2,3,4,4a,5,7a,8-octahydropyrido[4,3-d]carbazol-6(7H)-one (660 mg, 1.57 mmol, 1 eq.) in methanol (15 ml) and tetrahydrofuran (5 ml) at room temperature was added palladium hydroxide 20 % supported on carbon (66 mg) and the mixture was flushed with hydrogen and stirred under 4 atmosphere of hydrogen for 8 days. The mixture was filtered through a pad of celite and eluted with solution tetrahydrofuran/methanol (1-1). The volatiles were removed *in vacuo* and the residue was purified by column chromatography using flash silica gel, dichloromethane and methanol to afford an off-white solid; 0.21 g (45%[20])



CAS: /

Formula: $C_{19}H_{26}N_2O_1$

Molecular weight: 298.43 g/mol

MP: 133-134°C **Litt:** /

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.1 Hz, 1H, **H19**), 7.03 (td, *J* = 7.7, 1.2 Hz, 1H, **H17**), 6.65 (td, *J* = 7.5, 1.0 Hz, 1H, **H18**), 6.50 (d, *J* = 7.4 Hz, 1H, **H16**), 3.88 (s, 1H, **H14**), 3.82 (dd, *J* = 5.3, 1.2 Hz, 1H, **H13**), 3.35 (dd, *J* = 12.8,

[20] Almost half of starting material left after 8 days, not the best process.

4.2 Hz, 1H, **H2**), 3.16 (d, *J* = 12.1 Hz, 1H, **H22**), 2.86 (td, *J* = 12.7, 3.4 Hz, 1H, **H2**), 2.79 (d, *J* = 12.1 Hz, 1H, **H22**), 2.66 (dd, *J* = 11.9, 6.1 Hz, 1H, **H8**), 2.53 – 2.41 (m, 1H, **H4**), 2.22 (dd, *J* = 18.6, 4.6 Hz, 1H, **H5**), 2.01 – 1.90 (m, 2H, **H3** + **H5'**), 1.90 – 1.81 (m, 1H, **H9**), 1.60 (d, *J* = 12.6 Hz, 1H, **H3'**), 1.45 – 1.23 (m, 5H, **H9** + **H10** + **H11**), 0.93 (t, *J* = 7.1 Hz, 3H, **H12**).

^{13}C NMR (100 MHz, $CDCl_3$) δ 211.36 (**C6**), 150.51 (**C15**), 129.86 (**C20**), 128.62 (**C17**), 127.25 (**C19**), 117.89 (**C18**), 109.05 (**C16**), 65.37 (**C13**), 58.35 (**C22**), 50.42 (**C8**), 49.24 (**C21**), 46.26 (**C2**), 43.63 (**C5**), 37.62 (**C4**), 29.58 (**C10**), 27.86 (**C3**), 24.48 (**C9**), 23.02 (**C11**), 14.11 (**C12**).

IR (film, cm^{-1}): 3367 (N-H stretching), 2929 (C-H stretching), 2859 (C-H stretching), 1706 (C=O stretching of saturated cyclic 6-membered ring ketone), 1604 (C=C aromatic stretching), 1588 (C=C aromatic stretching), 1483 (CH_2 scissoring), 1466 (CH_3 asymmetric deformation), 1314 (C-N stretching), 1252 (C-N stretching), 909, 724 (C-H bending out of plan of ortho di-substituted aromatic ring).

HRMS m/z calculated for $C_{19}H_{27}N_2O_1$ $[M+H]^+$: 299.2123. Found: 299.2119.
HRMS m/z calculated for $C_{19}H_{26}N_2O_1{}^{23}Na_1$ $[M+Na]^+$: 321.1942. Found: 321.1935.